

## **Protocol and Protocol Amendments**

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113681 (MALARIA-063)  
Report (Immunogenicity and safety combined Month 3 and Month 8) Final

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Administrative change 1



**Clinical Study Protocol**

Sponsor:  
**GlaxoSmithKline Biologicals**  
Rue de l'Institut 89, 1330 Rixensart,  
Belgium

<b>Primary Study vaccine and number</b>	GlaxoSmithKline (GSK) Biologicals' candidate <i>Plasmodium falciparum</i> malaria vaccine RTS,S/AS01 <sub>E</sub> (257049)
<b>Other Study vaccines</b>	<ul style="list-style-type: none"><li>• GSK Biologicals' hepatitis B vaccine (Engerix-B™)</li><li>• GSK Biologicals' 10-valent pneumococcal conjugate vaccine (Synflorix™)</li><li>• GSK Biologicals' oral live attenuated human rotavirus vaccine (Rotarix™)</li><li>• GSK Biologicals' oral polio vaccine (Polio Sabin™)</li><li>• DTPa/Hib vaccine (Infanrix™Hib)</li></ul>
<b>eTrack study number and Abbreviated Title</b>	113681 (Malaria-063)
<b>Date of protocol</b>	Final: 27 August 2010
<b>Date of administrative change</b>	<i>Administrative change 1 Final, 22 November 2011</i>
<b>Title</b>	Immunogenicity of the hepatitis B antigen of the GSK Biologicals' candidate malaria vaccine (257049).
<b>Detailed Title</b>	Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01 <sub>E</sub> candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.
<b>Co-ordinating authors</b>	PPD [redacted] scientific writer Project Manager Scientific Writer
<b>Contributing authors</b>	<ul style="list-style-type: none"><li>• PPD [redacted] <b>Global Study Manager</b></li><li>• PPD [redacted] Manager Safety Physician, Clinical Safety and Pharmacovigilance</li><li>• PPD [redacted] Global Study Manager</li><li>• [redacted] Clinical Immunology Read Outs Manager, R&amp;D</li><li>• PPD [redacted] Director, Global Clinical R&amp;D</li><li>• PPD [redacted] Bio-Statistician Manager, Global Clinical R&amp;D</li><li>• PPD [redacted] WHO/TDR fellow</li><li>• PPD [redacted] Clinical Data Management</li></ul>

*List continues overleaf*

**GSK Biologicals' Protocol DS v 13.1**

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Clinical Regulatory, Clinical Reg. & Labelling
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**Protocol Administrative change 1 Sponsor Signatory Approval**

**eTrack study number and** 113681(Malaria-063)

**Abbreviated Title**

**Date of administrative** *Administrative change 1 Final, 22 November 2011*  
**change**

**Detailed Title** Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01<sub>E</sub> candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.

**Sponsor signatory** Johan Vekemans, Director,  
Clinical Development, Malaria Vaccines

**Signature**

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**Date**

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## Protocol Administrative Change 1 Rationale

<b>Administrative change number:</b>	Administrative change 1
<b>Rationale/background for changes:</b>	
Some typographical errors were corrected for clarity:	
<ul style="list-style-type: none"> <li>• In Synopsis table 1 and in Table 3: the footnote of Rotarix in the RE[RoP]s group was corrected (should be footnote b and not c)</li> <li>• The volume of the reconstituted Rotarix is 1.0 ml. It was erroneously recorded as 1.5 ml in table 15 and in the heading of section 6.3.5. and has been corrected.</li> <li>• Infanrix is administered in the right deltoid as described in table 16. In section 6.3.4. this was mistakenly mentioned in the left deltoid and has been corrected.</li> </ul>	
<b>Corrected text has been indicated in <i>bold italics</i>, deletions are indicated by strikethrough.</b>	

## **Protocol Administrative change 1 Investigator Agreement**

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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**eTrack study number and  
Abbreviated Title** 113681(Malaria-063)

**Date of administrative  
change** *Administrative change 1 Final, 22 November 2011*

**Detailed Title** Phase III randomized, open, controlled study to  
evaluate the immune response to the hepatitis B  
antigen of the RTS,S/AS01<sub>E</sub> candidate vaccine, when  
administered as primary vaccination integrated into  
an EPI regimen to infants living in sub-Saharan  
Africa.

**Investigator name**

**Signature**

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**Date**

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## SYNOPSIS

**Detailed Title** Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01<sub>E</sub> candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.

**Indication  
(Study population)** Primary immunization of healthy male and female infants aged 8 to 12 weeks against *P. falciparum* malaria and hepatitis B, if eligible according to inclusion and exclusion criteria.

**Rationale for the study and study design** The RTS,S/AS01<sub>E</sub> candidate malaria vaccine is being developed for the routine immunization of infants and children living in malaria-endemic areas as part of the WHO Expanded Program on Immunization (EPI). The candidate vaccine consists of sequences of the *Plasmodium falciparum* circumsporozoite (CS) protein and hepatitis B surface antigen (HBsAg) adjuvanted with AS01<sub>E</sub> (containing proprietary liposomes, MPL and QS21 immunostimulants). This vaccine would provide protection against both malaria disease due to the malaria parasite *P. falciparum*, and hepatitis B. This study therefore aims to support the indication of RTS,S/AS01<sub>E</sub> candidate vaccine for primary immunization of infants against the hepatitis B virus infection.

This study is designed to:

- Evaluate the immune response to the hepatitis B antigen in recipients of RTS,S/AS01<sub>E</sub> versus recipients of a licensed hepatitis B vaccine, including memory response and the quality of the immune response.
- Evaluate the immune response to the antigens contained in a conjugate pneumococcal vaccine and in a rotavirus vaccine when administered concomitantly with RTS,S/AS01<sub>E</sub>, within the existing EPI schedules in African countries.
- Demonstrate consistency of the hepatitis B response induced by RTS,S/AS01<sub>E</sub> candidate vaccine produced at the intended scale for commercial production of RTS,S bulk antigen.



## Objectives

### Primary

- To demonstrate in terms of antibody response to the HBs antigen, the non-inferiority of RTS,S/AS01<sub>E</sub> to a primary vaccination regimen of a licensed hepatitis B vaccine (Engerix-B) integrated into an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the difference in percent seroprotection below 5% between recipients of licensed hepatitis B vaccine (Engerix-B) and recipients of RTS,S/AS01<sub>E</sub> vaccine.*

### Secondary

#### Immunogenicity

- To demonstrate the non-inferiority of antibody responses to the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the GMC ratios of 10 pneumococcal serotypes titers (measured with an ELISA test), is below a limit of 2 for the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody responses to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), measured by ELISA and OPA, when the pneumococcal conjugate vaccine is co-administered with and without RTS,S/AS01<sub>E</sub> as part of an EPI-regimen.
- To describe the antibody response to the Protein D (PD) component of the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.
- To demonstrate the non-inferiority of antibody response to the rotavirus vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 2, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the geometric mean titers (GMT) ratios of rotavirus antibodies (IgA) titers is below 2 for the rotavirus vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody response to the rotavirus antigen

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when co-administered with and without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

- To describe the antibody response to the HBs antigen, induced by RTS,S/AS01<sub>E</sub> when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- To describe the antibody response to the HBs RF1 epitope, induced by RTS,S/AS01<sub>E</sub> when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- To describe the antibody response to the CS antigen when RTS,S/AS01<sub>E</sub> is co-administered with a pneumococcal conjugate vaccine as part of an EPI regimen.
- To describe the antibody response to the CS antigen when RTS,S/AS01<sub>E</sub> is co-administered with a rotavirus vaccine as part of an EPI regimen.
- To demonstrate the lot-to-lot consistency in terms of anti-HBs immunogenicity between three commercial lots of the RTS,S/AS01<sub>E</sub> candidate malaria vaccine.

*Criteria for consistency: one month post Dose 3 of RTS,S/AS01<sub>E</sub>, the two-sided 95% confidence interval (CI) of the geometric mean titer (GMT) ratio between all pairs of lots are within [0.5, 2].*

- To demonstrate the non-inferiority of antibody response to the acellular B pertussis antigens of the DTPa/Hib vaccine when co-administered with RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the GMT ratios of anti-PT, anti-FHA, anti-PRN antibody titers, is below a limit of 2 for the DTPa/Hib vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody response to acellular B pertussis antigens pre- and post-vaccination when a DTPa/Hib vaccine is co-administered with RTS,S/AS01<sub>E</sub> as part of an EPI-regimen.

***Immunogenicity follow-up***

- To describe the long-term antibody response to the HBs antigen induced by RTS,S/AS01<sub>E</sub>, compared to a primary vaccination regimen of a licensed hepatitis B vaccine when administered as a 3 doses schedule (0, 1, 2-month)

integrated into an EPI regimen.

- Evaluation of the antibody response to the HBs antigen induced by a booster dose of a licensed hepatitis B vaccine.
- Evaluation of the antibody response to HBs RF1 like antigen induced by a booster dose of a licensed hepatitis B vaccine.
- To describe the long-term antibody response to the CS antigen induced by RTS,S/AS01<sub>E</sub>, when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- Evaluation of the antibody response to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) induced by a booster dose of a licensed pneumococcal conjugate vaccine when co-administered with and without RTS,S/AS01<sub>E</sub>.

#### *Safety*

- Evaluation of the safety profile of the RTS,S/AS01<sub>E</sub> candidate malaria vaccine, when co-administered with a pneumococcal conjugate vaccine or a rotavirus vaccine integrated into an EPI regimen.

#### **Study design**

- **Experimental design:** Phase III, multi-center, open, randomized, controlled trial with 11 study groups.
- **Study population:** male and female infants, aged 8-12 weeks at the time of first vaccination, who are eligible based on inclusion and exclusion criteria.
- **Control:** *Engerix-B*
- **Treatment allocation:** Subjects will be randomized into 11 study groups in a 1:1:1 : 1:1:1 : 1:1:1 :3:3 ratio [this means 5 treatment groups of which the 3 RTS,S/AS01<sub>E</sub> groups will be randomized to receive 3 different lots].
- **Treatment groups and vaccination schedule:**  
The primary vaccination schedule for all treatment groups is presented in Synopsis Table 1. In the RTS,S arms, 3 doses of RTS,S/AS01<sub>E</sub> will be administered on a 0,1,2-month schedule. All groups will receive the measles vaccine 6 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. Yellow fever vaccine will be given according to local treatment regulations, at 6 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. All groups will receive *Synflorix* and *Infanrix/Hib* booster vaccinations at

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approximately 18 months of age (Visit 11), and an  
*Engerix-B* booster vaccination at 48 months after the third  
dose in the primary vaccination schedule of *Engerix-B*.

**Synopsis Table 1 Treatment groups**

Treatment Group	Study Group	Primary vaccination schedule	Number of subjects
REP[Ro] <sub>s</sub>	REP[Ro] <sub>s</sub> lot 1 REP[Ro] <sub>s</sub> lot 2 REP[Ro] <sub>s</sub> lot 3	RTS,S/AS01 <sub>E</sub> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Synflorix</i> <sup>a</sup> ) + <i>Rotarix</i> <sup>b</sup> staggered	141 (47+47+47)
RERo[P] <sub>s</sub>	RERo[P] <sub>s</sub> lot 1 RERo[P] <sub>s</sub> lot 2 RERo[P] <sub>s</sub> lot 3	RTS,S/AS01 <sub>E</sub> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Rotarix</i> <sup>c</sup> ) + <i>Synflorix</i> <sup>d</sup> staggered	141 (47+47+47)
RE[RoP] <sub>s</sub>	RE[RoP] <sub>s</sub> lot 1 RE[RoP] <sub>s</sub> lot 2 RE[RoP] <sub>s</sub> lot 3	RTS,S/AS01 <sub>E</sub> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> ) + staggered ( <i>Synflorix</i> <sup>d</sup> + <i>Rotarix</i> <sup>b</sup> )	141 (47+47+47)
HEP[Ro] <sub>s</sub>	HEP[Ro] <sub>s</sub>	<i>Engerix-B</i> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Synflorix</i> <sup>a</sup> ) + <i>Rotarix</i> <sup>b</sup> staggered	141
HERo[P] <sub>s</sub>	HERo[P] <sub>s</sub>	<i>Engerix-B</i> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Rotarix</i> <sup>c</sup> ) + <i>Synflorix</i> <sup>d</sup> staggered	141

a. Administration at Visit 2, Visit 4 and Visit 6

b. Administration at Visit 5 and Visit 7

c. Administration at Visit 4 and Visit 6

d. Administration at Visit 3, Visit 5 and Visit 7

- **Type of study:** self-contained
- **Data collection:** Where technically possible, this study will use electronic case report form (eCRF) by remote data entry (RDE) in preference to conventional paper case report form (CRF).
- **Duration of the study:** approximately 52 months per study participant, including a screening period and 49 months of follow-up after the third vaccination of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- **Epochs:**
  - Screening Epoch  
starting Visit 1 and ending before Visit 2 (Day 0)
  - Primary vaccination Epoch  
starting Visit 2 (Day 0) and ending at Visit 8 (Week 12)
  - Safety follow-up Epoch  
starting after Visit 8 (Week 12) and ending at Visit 9 (Month 8)
  - Immunogenicity follow-up 1 Epoch

starting after Visit 9 (Month 8); ending at Visit 13  
(Month 26)

- Immunogenicity follow-up 2 Epoch  
starting after Visit 13 (Month 26); ending at Visit 16  
(Month 51)

### **Screening of pregnant women**

- Pregnant women will be identified at antenatal clinics or in the community and will be informed about the study. If interested in participating they will be asked to sign a consent form for screening for hepatitis B or HIV infection.
- Infants born to mothers who are HBsAg positive and are therefore at high risk of vertical transmission of hepatitis B infection will be excluded from this trial. These infants will be offered a licensed hepatitis B vaccine in a schedule beginning at birth. Women who are tested positive for HBsAg with symptoms will be referred to an appropriate health care center.
- Infants born to mothers who are HIV positive will be excluded from this trial. Voluntary counselling and testing (VTC), highly active anti retroviral therapy (HAART) and prevention of mother-to-child transmission (PMCT) are available at the study center according to national policies.
- The site study team will ensure that insecticide treated bednet use is optimized in the study population.

### **Screening of infants**

- Mothers who were screened negative for HBsAg and HIV and who agree to let their child participate in the study will be invited for the screening visit (Visit 1).
- Prior to any other study procedures, the parents will be asked to sign/thumb-print a consent form to allow their child to participate in the trial.

### **Surveillance for safety**

- Each subject will be observed for at least 60 minutes after vaccination to evaluate and treat any acute adverse events (AEs).
- There will be a 7-day follow-up period (day of vaccination and 6 subsequent days) after each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines for

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recording of solicited AEs (+ any unsolicited AEs). On day of vaccination (day 0) the evaluation will be carried out by the study physician at the study center. On days 1, 2, 3, 4, 5 and 6 after vaccination, trained study personnels will visit the children to record solicited AEs and any unsolicited AEs.

- There will be a 30-day follow-up period (day of vaccination and 29 subsequent days) after each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines for reporting unsolicited adverse events.
- All SAEs will be reported until 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- This study will be overseen by a formally constituted IDMC operating under a charter.

**Blood sampling**

- Groups RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub> and HERo[P]<sub>s</sub> will have a total of 7 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*).
- Groups REP[Ro]<sub>s</sub> and HEP[Ro]<sub>s</sub> will have a total of 8 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 12, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*).
- Blood for safety evaluation will be collected at screening (Visit 1) to ensure healthy children are recruited.

**Surveillance for immunogenicity**

- Immune responses to the HBs antigen will be assessed at screening (Visit 1), at Visit 8 (one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*), at Visit 10 (Month 14), at Visit 13 (Month 26), at Visit 14 (Month 38), at Visit 15 (Month 50) and at Visit 16 (Month 51).
- Immune responses to the CS antigen will be assessed at screening (Visit 1), at Visit 8 (one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*), at Visit 10 (Month 14), at Visit 13 (Month 26), at Visit 14 (Month 38) and at Visit 15 (Month 50).
- Immune response to the 10 pneumococcal serotypes will be assessed at one month post Dose 3 of pneumococcal conjugate vaccine with RTS,S/AS01<sub>E</sub> co-administration (Visit 8) and one month post booster dose of

pneumococcal conjugate vaccine (Visit 12).

- Immune response to rotavirus antigen will be assessed at one month post Dose 2 of rotavirus vaccine with RTS,S/AS01<sub>E</sub> co-administration (Visit 8).

#### **Statistical analysis**

- The primary analysis will be performed on data collected up to Visit 8 (1 month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*) and will include primary and secondary immunogenicity and safety endpoints. Results will be reported in a final study report.
- A safety analysis will be performed on data (SAEs) collected until 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B* (Visit 9) and will be reported in an annex report.
- An immunogenicity analysis based on data collected until Visit 13 (Month 26) will include anti-CS and anti-HBs antibody responses and will be reported in an annex report.
- The final analysis will be performed on further safety and immunogenicity data collected up to the last study visit (Visit 16), 51 months following the administration of the first dose of study vaccine. Results will be presented in an annex report.

**Number of subjects** A total of 705 subjects will be enrolled (141 per group), in order to have at least 600 evaluable subjects (approximately 120 per group).

#### **Endpoints** **Primary: immunogenicity**

- Non-inferiority of the immune response to the hepatitis B antigen induced by RTS,S/AS01<sub>E</sub> vaccine versus a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.

#### **Secondary**

##### ***Immunogenicity***

- Non-inferiority of the immune response to the 10 pneumococcal serotype antigens when pneumococcal conjugate vaccine is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.

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- Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response to the 10 pneumococcal serotype antigens of the pneumococcal conjugate vaccine, when given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
  - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response against the protein D (PD) component of the pneumococcal antigen.
  - Anti-PD antibody titers one month post Dose 3 of pneumococcal conjugate vaccine.
- Non-inferiority of the immune response to the rotavirus antigen when the rotavirus vaccine is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.
- Immune response to the rotavirus antigen of the rotavirus vaccine, when given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.
- Immune response to hepatitis B antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
  - Anti-HBs RF1 like antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- Immune response to the CS antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> when given as part of an EPI regimen with and without pneumococcal conjugate vaccine co-administration.
  - Anti-CS antibody titers one month post Dose 3 of



RTS,S/AS01<sub>E</sub>.

- Immune response to the CS antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> when given as part of an EPI regimen with and without rotavirus co-administration.
  - Anti-CS antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Lot-to lot consistency for immunogenicity of three lots of the investigational vaccine RTS,S/AS01<sub>E</sub>.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Non-inferiority of the immune response to the acellular B pertussis antigens of the DTPa/Hib vaccine when given with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-acellular B pertussis (BPT) antibody titers (anti-PT, anti-FHA, anti-PRN) at screening and one month post Dose 3 of the DTPa/Hib vaccine.
- Immune response to the acellular B pertussis antigens of the DTPa/Hib vaccine (anti-PT, anti-FHA, anti-PRN) when given with RTS,S/AS01<sub>E</sub>.
  - Anti-acellular B-Pertussis (BPT) antibody titers (anti-PT, anti-FHA, anti-PRN) at screening and one month post Dose 3 of the DTPa/Hib vaccine.

***Immunogenicity follow-up***

- Immune response (on a long-term) to the hepatitis B antigen after a primary course of investigational vaccine RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers assessed at 12, 24, 36 and 48 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- Immune response to a booster dose of a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post booster dose of *Engerix-B*.
  - Anti-HBs RF1 like antibody titers one month post booster dose of *Engerix-B*.
- Immune response (on a long-term) to the CS-antigen after a primary course of the investigational vaccine RTS,S/AS01<sub>E</sub>.
  - Anti-CS antibody titers assessed 12, 24, 36 and 48

months post Dose 3 of RTS,S/AS01<sub>E</sub>.

- Immune response to a booster dose of pneumococcal conjugate vaccine when primary vaccination is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti- pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post booster dose of pneumococcal conjugate vaccine.
  - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post booster dose of pneumococcal conjugate vaccine.
  - Anti-protein D antibody titers one month post booster dose of pneumococcal conjugate vaccine.

### *Safety*

- For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro]<sub>s</sub>, RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub>, HEP[Ro]<sub>s</sub> and HERo[P]<sub>s</sub>), to describe the occurrence of solicited general and local adverse events (AEs) over a 7-day follow-up period (day of vaccination and 6 subsequent days) after the first, second and third doses of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
- For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro]<sub>s</sub>, RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub>, HEP[Ro]<sub>s</sub> and HERo[P]<sub>s</sub>), to describe the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after the first, second and third doses of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
- To describe the occurrence of serious adverse events (SAEs).
  - SAEs from the time of first vaccination until 3 month post Dose 1 (Visit 8) of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - SAEs from the time of first vaccination until 8 month post Dose 1 (Visit 9) of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Fatal SAEs from study start until study end.
  - Immune mediated disorders (IMDs) from study start until study end.

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## LIST OF ABBREVIATIONS

<b>AE</b>	Adverse Event
<b>ALT</b>	Alanine Aminotransferase
<b>anti-CS</b>	Antibody to the <i>Plasmodium falciparum</i> circumsporozoite (CS) repeat domain
<b>anti-HBs</b>	Antibody to the hepatitis B surface antigen
<b>anti-HBs RF1</b>	Antibody to the hepatitis B RF1 surface antigen
<b>anti-BPT</b>	Anti Bordetella Pertussis antibody
<b>ATP</b>	According To Protocol
<b>BPT</b>	<i>Bordetella pertussis</i>
<b>CCID<sub>50</sub></b>	Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
<b>CI</b>	Confidence Interval
<b>CRF/eCRF</b>	Case Report Form/electronic Case Report Form
<b>CS</b>	Circumsporozoite protein of <i>Plasmodium falciparum</i>
<b>DTPa/Hib</b>	Diphtheria, Tetanus, Pertussis (acellular) and <i>Haemophilus influenzae</i> type b conjugate vaccine
<b>ELISA</b>	Enzyme-Linked Immunosorbent Assay
<b>EMA</b>	European Medicines Agency
<b>EPI</b>	Expanded Program on Immunization
<b>EU/ml</b>	ELISA Unit per milliliter
<b>FDA</b>	Food and Drug Administration, United States
<b>GCP</b>	Good Clinical Practice
<b>GMC</b>	Geometric Mean Concentration
<b>GMT</b>	Geometric Mean Titer
<b>GSK</b>	GlaxoSmithKline
<b>HAART</b>	Highly Active Anti Retroviral Therapy
<b>HBsAg</b>	Hepatitis B surface antigen
<b>HBV</b>	Hepatitis B virus
<b>Hep B</b>	Hepatitis B
<b>HEP[Ro]<sub>s</sub></b>	Children to receive 3 doses of licensed hepatitis B vaccine with co-administration of DTPa/Hib and Polio Sabin EPI vaccines and co-administration of pneumococcal conjugate vaccine. Rotavirus vaccine will be given in a staggered way.

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<b>HERo[P]<sub>s</sub></b>	Children to receive 3 doses of licensed hepatitis B vaccine with co-administration of DTPa/Hib and Polio Sabin EPI vaccines and co-administration of rotavirus vaccine. Pneumococcal conjugate vaccine will be given in a staggered way.
<b>Hib</b>	<i>Haemophilus influenzae</i> type b
<b>HIV</b>	Human Immunodeficiency Virus
<b>ICF</b>	Informed Consent Form
<b>ICH</b>	International Conference on Harmonisation
<b>IDMC</b>	Independent Data Monitoring Committee
<b>IEC</b>	Independent Ethics Committee
<b>IgA</b>	Immunoglobulin A
<b>IM</b>	Intramuscular
<b>IMD</b>	Immune-Mediated Disorders
<b>IPD</b>	Invasive Pneumococcal Disease
<b>IRB</b>	Institutional Review Board
<b>IU</b>	International Unit
<b>kg</b>	Kilogram
<b>LAR</b>	Legally Acceptable Representative
<b>LSM</b>	Local Safety Monitor
<b>mAb</b>	Monoclonal antibody
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>mg</b>	Milligram
<b>ml</b>	Milliliter
<b>MPL</b>	3-deacylated Monophosphoryl Lipid A
<b>OPA</b>	Opsonophagocytic Assay
<b>OPV</b>	Oral Polio Vaccine
<b>PCV</b>	Pneumococcal Conjugate Vaccine
<b>PD</b>	Protein D, a 42 kD cell-surface lipoprotein which is highly conserved among capsulated and unencapsulated strains of <i>Haemophilus influenzae</i>
<b><i>P. falciparum</i></b>	<i>Plasmodium falciparum</i>
<b>PFS</b>	Pre-filled syringe
<b>PI</b>	Principal Investigator
<b>PMCT</b>	Prevention of mother-to-child transmission of HIV infection

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<b>QS21</b>	‘ <i>Quillaja saponaria</i> 21’: a triterpene glycoside purified from the bark of the soap bark tree, <i>Quillaja saponaria</i>
<b>RAP</b>	Report and Analysis Plan
<b>RCC</b>	Reverse Cumulative Curves
<b>RDE</b>	Remote Data Entry
<b>REP[Ro]<sub>s</sub></b>	Children to receive 3 doses of RTS,S/AS01 <sub>E</sub> with co-administration of DTPa/Hib and Polio Sabin EPI vaccines and co-administration of pneumococcal conjugate vaccine. Rotavirus vaccine will be given in a staggered way.
<b>RERo[P]<sub>s</sub></b>	Children to receive 3 doses of RTS,S/AS01 <sub>E</sub> with co-administration of DTPa/Hib and Polio Sabin EPI vaccines and co-administration of rotavirus vaccine. Pneumococcal conjugate vaccine will be given in a staggered way.
<b>RE[RoP]<sub>s</sub></b>	Children to receive 3 doses of RTS,S/AS01 <sub>E</sub> with co-administration of DTPa/Hib and Polio Sabin EPI vaccines. Rotavirus vaccine and pneumococcal conjugate vaccine will be given in a staggered way.
<b>RF1 mAb</b>	RF1 Monoclonal Antibody
<b>RTS,S</b>	Particulate antigen, containing both RTS and HBs proteins
<b>SAE</b>	Serious Adverse Event
<b>SBIR</b>	Internet Based Randomization System
<b>SDV</b>	Source Document Verification
<b>SOP</b>	Standard Operating Procedure
<b>SP</b>	Seropositive
<b>SPM</b>	Study Procedures Manual
<b>TVC</b>	Total Vaccinated Cohort
<b>VCT</b>	Voluntary Counselling and Testing
<b>WBC</b>	White blood cells
<b>WHO</b>	World Health Organization

## GLOSSARY OF TERMS

<b>Adverse event:</b>	<p>Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.</p>
<b>Blinding:</b>	<p>A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.</p>
<b>Child in care:</b>	<p>A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.</p>
<b>Independent Data Monitoring Committee:</b>	<p>The IDMC is an independent committee appointed to oversee ethical and safety aspects of the conduct of the study.</p>
<b>Eligible:</b>	<p>Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.</p>
<b>Epoch:</b>	<p>An epoch is a well defined part of a protocol that covers a set of consecutive time-points. Generally, an epoch is self-contained and allows to perform a data analysis to address some of the trial objectives (e.g. primary, booster, yearly follow-ups ...).</p>

<b>eTrack:</b>	GSK's tracking tool for clinical trials.
<b>Evaluable:</b>	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
<b>Investigational vaccine/product:</b> <b>(Synonym of Investigational Medicinal Product)</b>	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
<b>Local Safety Monitor:</b>	The Local Safety Monitor is an experienced physician based in-country who will be of support to the study investigators and act as a link between the investigators and the IDMC.
<b>Medical Monitor:</b>	An individual medically qualified to assume the responsibilities of the Sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
<b>Randomisation:</b>	Process of random attribution of treatment to subjects in order to reduce bias of selection.
<b>Serious Adverse Event:</b>	<p>A serious adverse event (SAE) is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> <li>a. results in death;</li> <li>b. is life-threatening;</li> <li>c. requires hospitalization or prolongation of existing hospitalization;</li> <li>d. results in disability/incapacity;</li> <li>e. adverse events of specific interest</li> </ul> <p>NB: AEs of specific interest include <b>all seizures occurring within a 30-day period of vaccination and immune-mediated disorders</b>. Key information pertaining to seizures occurring within 7 days of vaccination will be documented in the CRF/eCRF [refer to <a href="#">Bonhoeffer</a>, 2004]. AEs of specific interest to be reported as SAEs also include specific auto-immune diseases and other immune mediated disorders as listed in section <a href="#">8.2.2.5</a>.</p> <p>Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other</p>

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situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias.

<b>Site Monitor:</b>	An individual assigned by the Sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
<b>Solicited adverse event:</b>	Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
<b>Subject:</b>	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control.
<b>Subject number:</b>	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
<b>Treatment:</b>	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
<b>Unsolicited adverse event:</b>	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
<b>Vaccine number:</b>	A number identifying a vaccine to a subject, according to the study randomization or treatment allocation.

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## TRADEMARKS

The following trademarks are used in the present protocol.

**Note:** In the body of the Protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the subscript symbol <sup>TM</sup> or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Engerix-B <sup>TM</sup>	Hepatitis B vaccine
Infanrix <sup>TM</sup> Hib	Diphtheria, tetanus, acellular pertussis and Haemophilus Influenza type B vaccine
Polio Sabin <sup>TM</sup>	Oral poliovirus vaccine
Rotarix <sup>TM</sup>	Rotavirus vaccine
Synflorix <sup>TM</sup>	10-valent pneumococcal conjugate vaccine with protein D, diphtheria toxoid and tetanus carriers and containing pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F

## 1. INTRODUCTION

### 1.1. Background

GlaxoSmithKline (GSK) Biologicals is developing a pre-erythrocytic *Plasmodium falciparum* malaria vaccine (RTS,S/AS01<sub>E</sub> vaccine) for routine immunization of infants and children living in malaria-endemic areas as part of the Expanded Program of Immunization (EPI).

The RTS,S antigen is a hybrid antigen in which a portion of the circumsporozoite (CS) protein (repeat region (R) + T-cell epitopes (T)) is fused to a hepatitis B surface antigen (HBs Ag). This fused antigen, called RTS, is expressed together with an unfused HBs Ag in yeast. The RTS,S antigen is adjuvanted with GSK's proprietary Adjuvant System AS01 (liposome formulation with MPL and QS21 immunostimulants). By way of its recombinant antigen, RTS,S/AS01<sub>E</sub> offers protection against malaria disease due to *P. falciparum* and induces a good antibody response against infection with hepatitis B virus (HBV).

In studies completed to date, the RTS,S/AS candidate malaria vaccines consistently demonstrated efficacy with promising safety profile when administered to infants and young children in co-administrations with routine EPI vaccines.

Phase II evaluations of the RTS,S/AS vaccines have shown that both AS02 and AS01 pediatric formulations induce strong immune response to the S-antigen in RTS,S which is adequate to offer protection against hepatitis B infection [Malaria-046 Report ([GSK data on file](#)), 2008]. The antibody response to hepatitis B antigen induced by RTS,S/AS vaccines when administered to children [Malaria-026 Report ([GSK data on file](#)), 2006; Malaria-040 Report ([GSK data on file](#)), 2009] compared favourably with that of a licensed hepatitis B vaccine (*Engerix-B*), with anti-HBs seroprotection level (SP) after a 3-dose course of RTS,S/AS02 above 95%, which is in line with the World Health Organisation's position on SP level to be reached after Hepatitis B vaccination [[WHO](#), 2009]. In addition, compared with a licensed Hepatitis B vaccine, there is evidence of improved persistence of circulating antibodies following 3 doses of RTS,S/AS02 [Malaria-026 Report ([GSK data on file](#)), 2006; Malaria-038 Report ([GSK data on file](#)), 2008].

GSK Biologicals intends to seek an indication of prevention of hepatitis B for its RTS,S/AS01<sub>E</sub> vaccine considering that Hepatitis B immunization is a policy recommended by the World Health Organisation which is being implemented in EPI programmes. [[WHO](#), 2008].

Following recent recommendation by the WHO, [[WHO](#), 1999; [WHO](#), 2007] it is expected that pneumococcal and rotavirus vaccinations will be widely implemented in EPI programmes in the near future. Therefore GSK Biologicals intends to explore their interactions when co-administered with RTS,S/AS01<sub>E</sub> vaccine within EPI schedule.



Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of the candidate vaccine RTS,S/AS01<sub>E</sub>.

## 1.2. Rationale for the study and study design

### 1.2.1. Rationale for the study

This study aims to provide key information required to support the indication of the RTS,S/AS01<sub>E</sub> candidate vaccine for primary immunization of infants against the hepatitis B virus.

It is therefore designed to:

- Evaluate the immune response to the hepatitis B antigen in recipients of RTS,S/AS01<sub>E</sub> versus recipients of a licensed hepatitis B vaccine, including memory response and the quality of the immune response.
- Evaluate the immune response to the antigens contained in a conjugate pneumococcal vaccine and in a rotavirus vaccine when administered concomitantly with RTS,S/AS01<sub>E</sub>, within the existing EPI schedules in African countries.
- Demonstrate consistency of the hepatitis B response induced by RTS,S/AS01<sub>E</sub> candidate vaccine produced at the intended scale for commercial production of RTS,S bulk antigen.

### 1.2.2. Rationale for the hepatitis B vaccination in Africa

Hepatitis B is an infection of the liver due to hepatitis B virus (HBV); it is an important public health problem across the developing world. World-wide approximately 350 million people carry HBV and about 1 million chronic carriers die annually [Vryheid 2001]. Sub-Sahara Africa has approximately 50 million of HBV carriers, the second largest population after Asia [Burnett, 2005]. The likelihood of the infection becoming chronic is dependent upon the age at infection: 90% if infected in infancy, 30% to 50% if infected between the ages of 1 to 4 years, and low in adulthood. For those that become chronically infected during childhood, the risk of death from HBV-related liver cancer or cirrhosis in adult life is approximately 25% [WHO, 2008].

This information emphasizes the importance of hepatitis B vaccination in infants of sub-Saharan African countries.

#### 1.2.2.1. Evaluation of memory response to the HBs antigen

The persistence of the immune response to the HBs antigen of the candidate malaria vaccine will be tested at yearly intervals over a 4 years follow-up. To evaluate the memory response to HBs antigen, an additional dose of *Engerix-B* will be administered 4 years post Dose 3 to all study subjects. HBs antibody titers will be measured one month post administration of this additional dose of hepatitis B vaccine.

**1.2.3. Rationale for the evaluation of co-administration with a conjugate pneumococcal vaccine**

The WHO estimates that, annually, at least 1 million deaths worldwide are attributable to pneumococcal infections, recommending that pneumococcal vaccination of infants and children would reduce this burden [WHO, 1999]. GSK pneumococcal vaccine (*Synflorix*) is expected to protect against pneumococcal disease, in particular pneumococcal strains (serotypes 1, 5 and 7F) that are known to be responsible for a significant proportion of invasive pneumococcal disease (IPD) [Hausdorff, 2001].

Since spring 2009, GSK Biologicals' 10-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate (10Pn-PD-DiT) vaccine has been licensed in the European Union, Canada, Australia and several other countries worldwide and is marketed under the trademark of *Synflorix*. *Synflorix* is also prequalified by WHO.

It is presumed that in the near future pneumococcal conjugate vaccine will be widely implemented as EPI vaccines across sub-Saharan Africa.

**1.2.4. Rationale for the evaluation of co-administration with a rotavirus vaccine**

The WHO recommends the inclusion of rotavirus vaccination into the national immunization programmes as rotavirus vaccines have shown protection against severe rotavirus disease and against rotavirus diarrhoea of any severity. In Malawi and South Africa, vaccine efficacy against severe rotavirus disease in infants was respectively of 49% and 77% [Madhi, 2010]. However, due to the large burden of disease, efficacy of this level will translate into important public health benefits. The GSK Biologicals licensed rotavirus vaccine (*Rotarix*) provides significant broad protection against diverse circulating rotavirus strains. *Rotarix* received prequalification by WHO. It is presumed that in the near future a rotavirus vaccine would be widely implemented as EPI vaccines across sub-Saharan Africa [WHO, 2007].

**2. OBJECTIVES****2.1. Primary objective: immunogenicity**

- To demonstrate in terms of antibody response to the HBs antigen, the non-inferiority of RTS,S/AS01<sub>E</sub> to a primary vaccination regimen of a licensed hepatitis B vaccine (*Engerix-B*) integrated into an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the difference in percent seroprotection below 5% between recipients of licensed hepatitis B vaccine (Engerix-B) and recipients of RTS,S/AS01<sub>E</sub> vaccine.*

Refer to Section 10.1 for the definition of the primary endpoint.

## 2.2. Secondary objectives

### *Immunogenicity*

- To demonstrate the non-inferiority of antibody responses to the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the GMC ratios of 10 pneumococcal serotypes titers (measured with an ELISA test), is below a limit of 2 for the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody responses to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), measured by ELISA and OPA, when the pneumococcal conjugate vaccine is co-administered with and without RTS,S/AS01<sub>E</sub> as part of an EPI-regimen.
- To describe the antibody response to the Protein D (PD) component of the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.
- To demonstrate the non-inferiority of antibody response to the rotavirus vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 2, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the geometric mean titers (GMT) ratios of rotavirus antibodies (IgA) titers is below 2 for the rotavirus vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody response to the rotavirus antigen when co-administered with and without RTS,S/AS01<sub>E</sub> as part of an EPI regimen.
- To describe the antibody response to the HBs antigen, induced by RTS,S/AS01<sub>E</sub> when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- To describe the antibody response to the HBs RF1 epitope, induced by RTS,S/AS01<sub>E</sub> when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- To describe the antibody response to the CS antigen when RTS,S/AS01<sub>E</sub> is co-administered with a pneumococcal conjugate vaccine as part of an EPI regimen.
- To describe the antibody response to the CS antigen when RTS,S/AS01<sub>E</sub> is co-administered with a rotavirus vaccine as part of an EPI regimen.
- To demonstrate the lot-to-lot consistency in terms of anti-HBs immunogenicity between three commercial lots of the RTS,S/AS01<sub>E</sub> candidate malaria vaccine.

*Criteria for consistency: one month post Dose 3 of RTS,S/AS01<sub>E</sub>, the two-sided 95% confidence interval (CI) of the geometric mean titer (GMT) ratio between all pairs of lots are within [0.5, 2].*

- To demonstrate the non-inferiority of antibody response to the acellular B pertussis antigens of the DTPa/Hib vaccine when co-administered with RTS,S/AS01<sub>E</sub> as part of an EPI regimen.

*Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the GMT ratios of anti-PT, anti-FHA, anti-PRN antibody titers, is below a limit of 2 for the DTPa/Hib vaccine when co-administered with versus without RTS,S/AS01<sub>E</sub>.*

- To describe the antibody response to acellular B pertussis antigens pre- and post-vaccination when a DTPa/Hib vaccine is co-administered with RTS,S/AS01<sub>E</sub> as part of an EPI-regimen.

#### ***Immunogenicity follow-up***

- To describe the long-term antibody response to the HBs antigen induced by RTS,S/AS01<sub>E</sub>, compared to a primary vaccination regimen of a licensed hepatitis B vaccine when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- Evaluation of the antibody response to the HBs antigen induced by a booster dose of a licensed hepatitis B vaccine.
- Evaluation of the antibody response to HBs RF1 like antigen induced by a booster dose of a licensed hepatitis B vaccine.
- To describe the long-term antibody response to the CS antigen induced by RTS,S/AS01<sub>E</sub>, when administered as a 3 doses schedule (0, 1, 2-month) integrated into an EPI regimen.
- Evaluation of the antibody response to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) induced by a booster dose of a licensed pneumococcal conjugate vaccine when co-administered with and without RTS,S/AS01<sub>E</sub>.

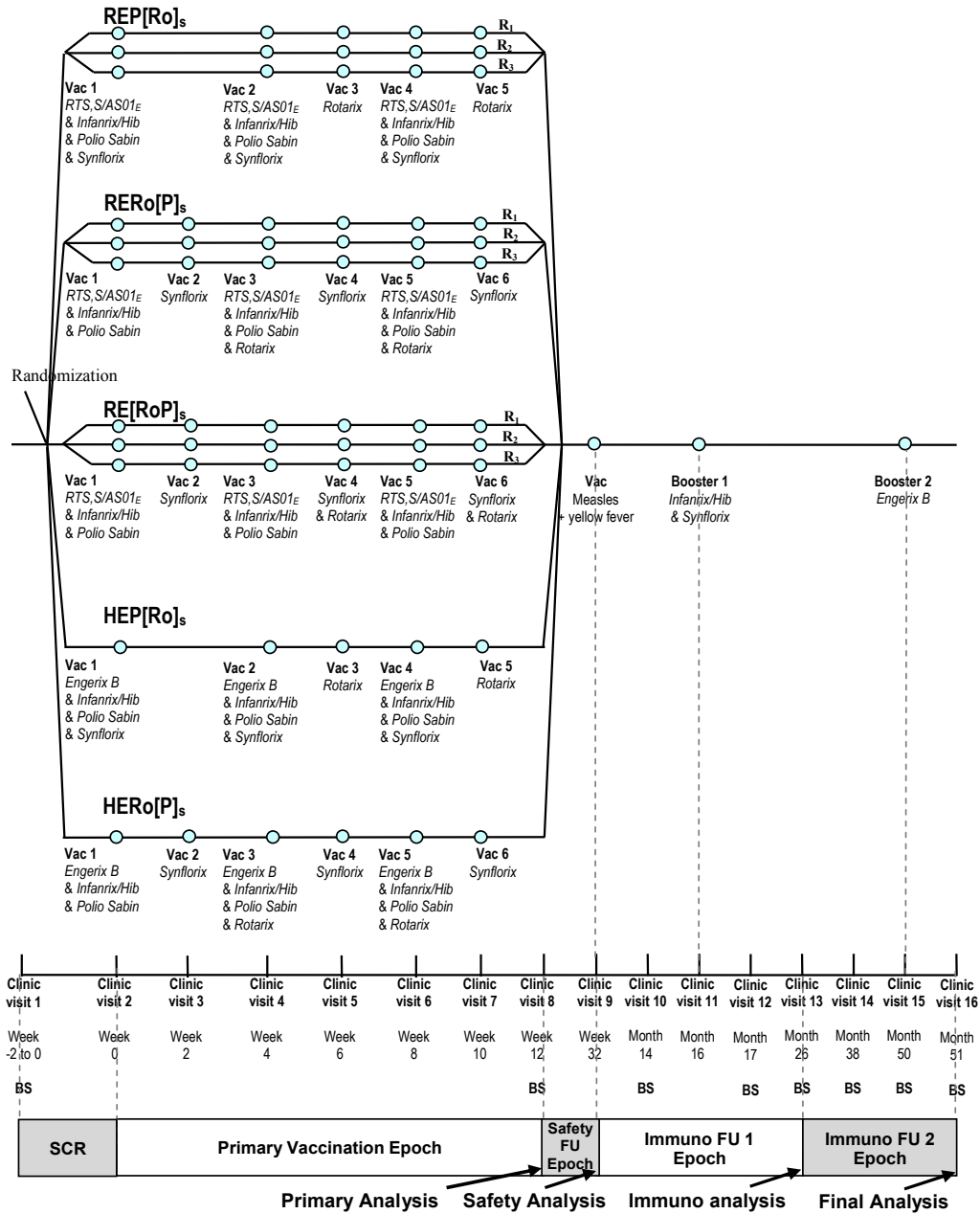
#### ***Safety***

- Evaluation of the safety profile of the RTS,S/AS01<sub>E</sub> candidate malaria vaccine, when co-administered with a pneumococcal conjugate vaccine or a rotavirus vaccine integrated into an EPI regimen.

Refer to Section 10.2 for the definition of the secondary endpoints.

## 3. STUDY DESIGN OVERVIEW

Figure 1 Study design diagram



Vac = vaccination; SCR = Screening Epoch; FU = Follow-up; BS = blood sample  
 R = RTS,S/AS01<sub>E</sub>; E = Infanrix/Hib + Polio Sabin EPI vaccines; P = pneumococcal conjugate vaccine (Synflorix);  
 Ro = Rotavirus vaccine (Rotarix); H = Hepatitis B vaccine (Engerix B);  
 R<sub>1</sub> = RTS,S/AS01<sub>E</sub> lot 1; R<sub>2</sub> = RTS,S/AS01<sub>E</sub> lot 2; R<sub>3</sub> = RTS,S/AS01<sub>E</sub> lot 3

- **Experimental design:** Phase III, multi-center, open, randomized, controlled trial with 11 study groups.
- **Study population:** male and female infants, aged 8-12 weeks at the time of first vaccination, who are eligible based on inclusion and exclusion criteria.
- **Control:** *Engerix-B*
- **Treatment allocation:** Subjects will be randomized into 11 study groups in a 1:1:1 : 1:1:1 : 1:1:1 :3:3 ratio [this means 5 treatment groups of which the 3 RTS,S/AS01<sub>E</sub> groups will be randomized to receive 3 different lots].
- **Treatment groups and vaccination schedule:**  
The primary vaccination schedule for all treatment groups is presented in [Table 3](#) and [Table 4](#). In the RTS,S arms, 3 doses of RTS,S will be administered on a 0, 1, 2-month schedule. All groups will receive the measles vaccine 6 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. Yellow fever vaccine will be given according to local treatment regulations, at 6 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. All groups will receive *Synflorix* and *Infanrix/Hib* booster vaccinations at approximately 18 months of age (Visit 11), and an *Engerix-B* booster vaccination at 48 months after the third dose of *Engerix-B* in the primary vaccination schedule.
- **Blinding:** open-label.

**Table 1 Blinding of study epochs**

Study Epochs	Blinding
Screening Epoch	open
Primary vaccination Epoch	open
Safety follow-up Epoch	open
Immunogenicity follow-up 1 Epoch	open
Immunogenicity follow-up 2 Epoch	open

- **Type of study:** self-contained.
- **Data collection:** Where technically possible, this study will use electronic case report form (eCRF) by remote data entry (RDE) in preference to conventional paper case report form (CRF).
- **Duration of the study:** approximately 52 months per study participant, including a screening period and 49 months follow-up after the third vaccination of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- **Epochs:**
  - Screening Epoch  
starting Visit 1 and ending before Visit 2 (Day 0)
  - Primary vaccination Epoch  
starting Visit 2 (Day 0) and ending at Visit 8 (Week 12)

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- Safety follow-up Epoch  
starting after Visit 8 (Week 12) and ending at Visit 9 (Month 18)
- Immunogenicity follow-up 1 Epoch  
starting after Visit 9 (Month 8) and ending at Visit 13 (Month 26)
- Immunogenicity follow-up 2 Epoch  
starting after Visit 13 (Month 26) and ending at Visit 16 (Month 51)

**Table 2 Study groups and epochs foreseen in the study**

Study Group	Number of subjects	Age (Min/Max)	Epochs				
			Screening Epoch	Primary vaccination Epoch	Safety follow-up Epoch	Immunogenicity follow-up 1 Epoch	Immunogenicity follow-up 2 Epoch
REP[Ro]s lot 1	47	8-12 weeks	x	x	x	x	x
REP[Ro]s lot 2	47	8-12 weeks	x	x	x	x	x
REP[Ro]s lot 3	47	8-12 weeks	x	x	x	x	x
RERo[P]s lot 1	47	8-12 weeks	x	x	x	x	x
RERo[P]s lot 2	47	8-12 weeks	x	x	x	x	x
RERo[P]s lot 3	47	8-12 weeks	x	x	x	x	x
RE[RoP]s lot 1	47	8-12 weeks	x	x	x	x	x
RE[RoP]s lot 2	47	8-12 weeks	x	x	x	x	x
RE[RoP]s lot 3	47	8-12 weeks	x	x	x	x	x
HEP[Ro]s	141	8-12 weeks	x	x	x	x	x
HERo[P]s	141	8-12 weeks	x	x	x	x	x

**Table 3 Treatment groups**

Treatment Group	Study Group	Primary vaccination schedule	Number of subjects
REP[Ro]s	REP[Ro]s lot 1 REP[Ro]s lot 2 REP[Ro]s lot 3	RTS,S/AS01E <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Synflorix</i> <sup>a</sup> ) + <i>Rotarix</i> <sup>b</sup> staggered	141 (47+47+47)
RERo[P]s	RERo[P]s lot 1 RERo[P]s lot 2 RERo[P]s lot 3	RTS,S/AS01E <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Rotarix</i> <sup>c</sup> ) + <i>Synflorix</i> <sup>d</sup> staggered	141 (47+47+47)
RE[RoP]s	RE[RoP]s lot 1 RE[RoP]s lot 2 RE[RoP]s lot 3	RTS,S/AS01E <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> ) + staggered ( <i>Synflorix</i> <sup>d</sup> + <i>Rotarix</i> <sup>b</sup> )	141 (47+47+47)
HEP[Ro]s	HEP[Ro]s	<i>Engerix-B</i> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Synflorix</i> <sup>a</sup> ) + <i>Rotarix</i> <sup>b</sup> staggered	141
HERo[P]s	HERo[P]s	<i>Engerix-B</i> <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> + <i>Rotarix</i> <sup>c</sup> ) + <i>Synflorix</i> <sup>d</sup> staggered	141

a. Administration at Visit 2, Visit 4 and Visit 6  
b. Administration at Visit 5 and Visit 7

c. Administration at Visit 4 and Visit 6  
d. Administration at Visit 3, Visit 5 and Visit 7

**Table 4 Treatment groups (primary vaccination)**

Vaccine name	REP[Ro] <sub>s</sub>			RERo[P] <sub>s</sub>			RE[RoP] <sub>s</sub>			HEP[Ro] <sub>s</sub>	HERo[P] <sub>s</sub>
	REP[Ro] <sub>s</sub> lot 1	REP[Ro] <sub>s</sub> lot 2	REP[Ro] <sub>s</sub> lot 3	RERo[P] <sub>s</sub> lot 1	RERo[P] <sub>s</sub> lot 2	RERo[P] <sub>s</sub> lot 3	RE[RoP] <sub>s</sub> lot 1	RE[RoP] <sub>s</sub> lot 2	RE[RoP] <sub>s</sub> lot 3	HEP[Ro] <sub>s</sub>	HERo[P] <sub>s</sub>
RTS,S/AS01 <sub>E</sub>	x	x	x	x	x	x	x	x	x		
Infanrix/Hib	x	x	x	x	x	x	x	x	x	x	x
Polio Sabin	x	x	x	x	x	x	x	x	x	x	x
Synflorix	x	x	x	x	x	x	x	x	x	x	x
Rotarix	x	x	x	x	x	x	x	x	x	x	x
Engerix-B										x	x

**Screening of pregnant women**

- Pregnant women will be identified at antenatal clinics or in the community and will be informed about the study. If interested in participating they will be asked to sign a consent form for screening for hepatitis B or HIV infection.
- Infants born to mothers who are HBsAg positive and are therefore at high risk of vertical transmission of hepatitis B infection will be excluded from this trial. These infants will be offered a licensed hepatitis B vaccine in a schedule beginning at birth. Women who are tested positive for HBsAg with symptoms will be referred to an appropriate health care center.
- Infants born to mothers who are HIV positive will be excluded from this trial. Voluntary counselling and testing (VTC), highly active anti retroviral therapy (HAART) and prevention of mother-to-child transmission (PMCT) are available at the study center according to national policies.
- The site study team will ensure that insecticide treated bednet use is optimized in the study population.

**Screening of infants**

- Mothers who were screened negative for HBsAg and HIV and who agree to let their child participate in the study will be invited for the screening visit (Visit 1).
- Prior to any other study procedures, the parents will be asked to sign/thumb-print a consent form to allow their child to participate in the trial.

**Surveillance for safety**

- Each subject will be observed for at least 60 minutes after vaccination to evaluate and treat any acute adverse events (AEs).
- There will be a 7-day follow-up period (day of vaccination and 6 subsequent days) after each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines for recording of solicited AEs (+ any unsolicited AEs). On day of vaccination (day 0) the evaluation will be carried out by the study physician at the study center. On days 1, 2, 3, 4, 5 and 6 after vaccination, trained study personnel will visit the children to record solicited AEs and any unsolicited AEs.



- There will be a 30-day follow-up period (day of vaccination and 29 subsequent days) after each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines for reporting unsolicited adverse events.
- All SAEs will be reported until 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- This study will be overseen by a formally constituted IDMC operating under a charter.

#### **Blood sampling**

- Groups RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub> and HERo[P]<sub>s</sub> will have a total of 7 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*).
- Groups REP[Ro]<sub>s</sub> and HEP[Ro]<sub>s</sub> will have a total of 8 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 12, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*).
- Blood for safety evaluation will be collected at screening (Visit 1) to ensure healthy children are recruited.

#### **Surveillance for immunogenicity**

- Immune responses to the HBs antigen will be assessed at screening (Visit 1), at Visit 8 (one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*), at Visit 10 (Month 14), at Visit 13 (Month 26), at Visit 14 (Month 38), at Visit 15 (Month 50) and at Visit 16 (Month 51).
- Immune responses to the CS antigen will be assessed at screening (Visit 1), at Visit 8 (one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*), at Visit 10 (Month 14), at Visit 13 (Month 26), at Visit 14 (Month 38) and at Visit 15 (Month 50).
- Immune response to the 10 pneumococcal serotypes will be assessed at one month post Dose 3 of pneumococcal conjugate vaccine with RTS,S/AS01<sub>E</sub> co-administration (Visit 8) and one month post booster dose of pneumococcal conjugate vaccine (Visit 12).
- Immune response to rotavirus antigen will be assessed at one month post Dose 2 of rotavirus vaccine with RTS,S/AS01<sub>E</sub> co-administration (Visit 8).

#### **Statistical analysis**

- The primary analysis will be performed on data collected up to Visit 8 (1 month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*) and will include primary and secondary immunogenicity and safety endpoints. Results will be reported in a final study report.
- A safety analysis will be performed on data (SAEs) collected until 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B* (Visit 9) and will be reported in an annex report.

- An immunogenicity analysis based on data collected until Visit 13 (Month 26) will include anti-CS and anti-HBs antibody responses and will be reported in an annex report.
- The final analysis will be performed on further safety and immunogenicity data collected up to the last study visit (Visit 16), 51 months following the administration of the first dose of study vaccine. Results will be presented in an annex report.

## **4. STUDY COHORT**

### **4.1. Number of subjects/centres**

A total of 705 subjects will be enrolled (141 per group), in order to have at least 600 evaluable subjects (approximately 120 per group).

Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

### **4.2. Overview of the recruitment plan**

This study is intended to be conducted in multiple centers in sub-Saharan Africa. Details of the geography, demographics, healthcare provision and relevant site-specific information for each center are provided in the study center specific document. Enrolment will be terminated when approximately 705 children have been recruited.

### **4.3. Inclusion criteria for enrolment**

All subjects must satisfy **ALL** the following criteria at study entry:

- A male or female infant aged between 8 and 12 weeks inclusive at the time of first vaccination.
- Signed or thumb-printed informed consent obtained from the parent(s)/LAR(s) of the child. Where parent(s)/LAR(s) are illiterate, the consent form will be countersigned by an independent witness.
- Subjects who the investigator believes that their parent(s)/LAR(s) can and will comply with the requirements of the protocol (e.g. return for follow-up visits).
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born to a mother who is HBsAg negative.
- Born to a mother who is HIV negative.
- Born after a normal gestation period of 36 to 42 weeks inclusive.

**4.4. Exclusion criteria for enrolment**

The following criteria should be checked at the time of study entry. If **ANY** exclusion criterion applies, the subject must not be included in the study:

- Child in care. Please refer to the [GLOSSARY OF TERMS](#) for the definition of child in care.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  on oral, axillary or tympanic setting, or  $\geq 38.0^{\circ}\text{C}$  on rectal setting.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Serious acute or chronic illness determined by clinical or physical examination and laboratory screening tests including, but not limited to:
  - Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
  - A family history of congenital or hereditary immunodeficiency.
  - Major congenital defects.
  - History of any neurologic disorders or seizures.
  - Moderate malnutrition at screening defined as weight for age Z-score less than -2.
- Laboratory screening tests out of range, specifically:
  - ALT above acceptable limit (i.e.  $> 60 \text{ IU/L}$ ).
  - Creatinine above acceptable limit (i.e.  $> 60 \mu\text{mol/L}$ ).
  - Hemoglobin below acceptable limit (i.e.  $< 8.0 \text{ g/dL}$ ).
  - Platelet count below acceptable limit (i.e.  $< 100 \times 10^3/\mu\text{L}$ ).
  - Total white cell count below acceptable limit (i.e.  $< 4.0 \times 10^3/\mu\text{L}$ ).

Note that screening laboratory tests must be performed within 14 days of Dose 1.

- Previous vaccination with diphtheria, tetanus, pertussis (whole-cell or acellular), *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, hepatitis B vaccine or rotavirus vaccines.
- Planned administration/administration of a licensed vaccine (i.e. a vaccine that is approved by one of the following authorities: FDA or EU member state or WHO [with respect to prequalification]) not foreseen by the study protocol within 7 days of the first dose of study vaccine.
- Use of a drug or vaccine that is not approved for that indication (by one of the following authorities: FDA or EU member state or WHO [with respect to

prequalification]) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.

- Administration of immunoglobulins and/or any blood products in the period between birth and Dose 1 and within the three months preceding planned vaccine administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immuno-suppressants or other immune-modifying drugs in the period between birth and Dose 1. For corticosteroids, this will mean prednisone  $\geq 0.5$  mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Concurrently participating in another clinical study at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Same sex twin (to avoid misidentification).
- Maternal death.
- History of allergic reactions (significant IgE-mediated events) or anaphylaxis to previous immunizations.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.
- Any other findings that the investigator feels would result in data collected being incomplete or of poor quality.
- Previous participation in any other malaria vaccine trial.

A list of criteria that may eliminate subjects from ATP analyses can be found in Sections [6.7.1](#), [6.8](#) and [10.4](#).

## **5. CONDUCT OF THE STUDY**

### **5.1. Regulatory and ethical considerations, including the informed consent process**

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH (International Conference on Harmonisation) Guideline for Good Clinical Practice (GCP) all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parent(s)/LAR(s) informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject's parent(s)/LAR(s) prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the Sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

## **5.2. Subject identification and randomisation of treatment**

The target will be to enrol approximately 705 eligible subjects. Subjects will be randomized to 11 study groups with age and study centre used as a minimization factor. The allocation ratio will be 1:1:1 : 1:1:1 : 1:1:1 : 3:3. This means 5 treatment groups of which the 3 RTS,S/AS01<sub>E</sub> groups will be randomized to receive 3 different lots.

### **5.2.1. Subject identification**

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study center.

**5.2.2. Randomisation of treatment****5.2.2.1. Randomisation of supplies**

The randomization will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in SAS® (Cary, NC, USA) by GSK Biologicals.

**5.2.2.2. Treatment allocation to the subject**

The treatment allocation at the investigator site will be performed using a central randomisation system on internet (SBIR). The vaccine numbers will be allocated by component. The randomisation algorithm will use a minimisation procedure accounting for centre.

When SBIR is not available, please refer to the SBIR user guide or the SPM for specific instructions.

After having checked the eligibility of the subject and obtaining the ICF form, the site staff in charge of the vaccination will access SBIR. Upon providing the subject identification number, the randomisation system will use the minimisation algorithm to determine the treatment group and the vaccine number to be used for the subject. Each vaccine number must be recorded in the CRF/eCRF on the Vaccine Administration form/screen.

**5.3. Method of blinding**

The study is open-label.

**5.4. General study aspects**

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

**5.4.1. Safety Monitoring Plan**

The ethical and safety aspects of the conduct of this trial are overseen by an independent data monitoring committee (IDMC) operating under a charter assisted by a local safety monitor (LSM).

**5.4.1.1. Independent data monitoring committee (IDMC)**

The role of the IDMC includes the review of the implementation and progress of the study. It provides initial, regular and closing advice on safety-related issues to GSK Biologicals. Its advice is based on the interpretation of study data with reference to the study protocol.

The IDMC will review the Protocol, Report and Analysis Plan (RAP). The IDMC will review all safety data available for the RTS,S/AS01<sub>E</sub> pediatric development plan. Meetings may be face to face or via teleconference. Meetings must be documented and minutes made available to the sponsors. The IDMC may, if deemed necessary, convene a meeting with, or request further information from the Principal Investigators, the Medical Monitor/LSMs and GSK Biologicals' or MVI's designated project representatives at any stage of the study.

The IDMC may recommend to the Sponsor to suspend the enrolment to the trial and/or vaccination based on their review of safety data arising in this trial or other relevant trials of the same product.

**5.4.1.2. Data Reviewed by the IDMC**

The IDMC will review the following safety data:

- All SAEs.

In addition, The IDMC will receive from the sponsor, GSK Biologicals:

- New information that may adversely affect the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments, informed consent changes or revisions or other documents originally submitted for review.
- All subsequent protocol administrative changes (for information).

**5.4.1.3. Local Safety Monitor (LSM)**

The overall role of the LSM (experienced clinicians based in-country) will be to support the clinical investigators and to act as a link between the investigators and the IDMC.

The LSM's role will include:

- Acting as the study volunteer's advocate.
- Promptly communicating relevant safety information to the IDMC.
- Providing advice to the investigators on whether a set of clinical circumstances in a study warrants formal notification to the IDMC.
- Liaising closely with the chair of the IDMC throughout the course of the trial.

**5.4.1.4. Data Reviewed by the LSM**

The relevant LSM will be informed by the investigator on an 'as received' basis of:

- All SAEs.
- All withdrawals of study subjects by the Principal Investigators (PIs) or the parent(s)/LAR(s) of a subject due to AEs within 2 weeks of vaccination.

**5.4.1.5. Process if the trial is suspended**

If the Principal Investigator or LSM suspends the trial at their site, they must immediately notify the IDMC, and GSK Biologicals (the study sponsor) via the contacts for safety reporting (refer to Section 8.3).

If the trial is suspended, the IDMC will review all available information and make a recommendation to the study sponsor (GSK Biologicals) whether to restart the trial or to stop the trial permanently.

It is the responsibility of the sponsor (GSK Biologicals) to make the decision whether or not the trial should be stopped permanently.

**5.4.1.6. Safety Review Team (SRT)**

A safety review team (SRT) at GSK Biologicals comprising a clinical safety physician, medical monitor and a statistician will review, on an ongoing basis, SAEs occurring during the trial. They will review all safety reports.

**5.5. Outline of study procedures**

The list of study procedures to be conducted is detailed in Table 5.



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Table 5 List of study procedures

Epoch	SCR		Primary vaccination										Sft FU	Immunogenicity FU1					Immunogenicity FU2		
STUDY MONTH	0			1			2			3	8	14	16	17	26	38	50	51			
STUDY WEEK	0			2	4		6	8		10	12	32									
STUDY DAY	-14 - 0	0	1-6	14	28	29-34	42	56	57-62	70											
Visit	1	2	a-f	3	4	g-l	5	6	m-r	7	8	9	10	11	12	13	14	15	16		
Informed consent	•																				
Assign subject number	•																				
Demographic data	•																				
Medical history	•	0																			
Check inclusion/exclusion criteria	•	0																			
Complete physical examination	•	0			0			0			0	0		0	0	0	0	0	0		
Measure/record length (less than 2 years of age) or height (equal or above 2 years of age)		•									•	•									
Measure/record weight	0	•			0			0			0	•									
Body temperature		•	0	•	•	0	•	•	0	•		0	0	•	0	0	0	•			
Check contraindications to vaccination		•		•	•		•	•		•		•		•				•			
Check warnings and precautions		•		•	•		•	•		•		•		•				•			
Randomisation		0																			
Recording of vaccine number		•		•	•		•	•		•				•				•			
Administer <i>Infanrix</i> /Hib vaccine (all groups)		•			•			•													
Administer Polio Sabin vaccine (all groups)		•			•			•													
Administer RTS,S/AS01E vaccine to groups REP[Ro]s, RERo[P]s and RE[RoP]s		•			•			•													
Administer <i>Engerix-B</i> vaccine to groups HEP[Ro]s and HERo[P]s		•			•			•													
Administer <i>Synflorix</i> vaccine to groups REP[Ro]s and HEP[Ro]s		•			•			•													
Administer <i>Synflorix</i> vaccine to groups RERo[P]s, RE[RoP]s and HERo[P]s					•			•		•											
Administer Rotarix vaccine to groups RERo[P]s and HERo[P]s					•			•													
Administer Rotarix vaccine to groups REP[Ro]s, RE[RoP]s and HEP[Ro]s								•		•											
Administer measles and yellow fever vaccine (all groups)												•									

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Epoch	SCR	Primary vaccination										Sft FU	Immunogenicity FU1					Immunogenicity FU2		
STUDY MONTH		0		1			2			3	8	14	16	17	26	38	50	51		
STUDY WEEK		0		2	4		6	8		10	12	32								
STUDY DAY	-14 - 0	0	1-6	14	28	29-34	42	56	57-62	70										
Visit	1	2	a-f	3	4	g-l	5	6	m-r	7	8	9	10	11	12	13	14	15	16	
Administer <i>Infanrix</i> /Hib vaccine and <i>Synflorix</i> booster (all groups)														•						
Administer <i>Engerix-B</i> booster (all groups)																		•		
Record any concomitant medication/vaccination		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Record any intercurrent medical conditions**		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Recording of solicited symptoms ***		• a	• a	• a	• a	• a	• a	• a	• a											
Recording of unsolicited symptoms		• b	• b	• b	• b	• b	• b	• b	• b	• b	• b									
Reporting of serious adverse events		•	•	•	•	•	•	•	•	•	•	•								
Reporting of SAEs related to study participation or any fatal SAE and immune mediated disorders	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Blood sampling for hemoglobin, WBC, platelets, ALT and Creatinine (all groups)	•																			
Blood sampling for HBs antibody determination (all groups)	•										•		•			•	•	•	•	•
Blood sampling for HBs RF1-like antibody determination (all groups)											•								•	
Blood sampling for CS antibody determination (all groups)	•										•		•			•	•	•		
Blood sampling for pneumococcal serotype antibody determination (ELISA + OPA + PD) (REP[Ro]s and HEP[Ro]s)											•			•						
Blood sampling for Rotavirus IgA antibody determination (RERo[P] <sub>s</sub> and HERo[P] <sub>s</sub> )											•									
Blood sampling for acellular B Pertussis (BPT) antibody determination (all groups)	•										•									
PRIMARY ANALYSIS											•									
SAFETY ANALYSIS												•								
IMMUNOGENICITY ANALYSIS																•				
FINAL ANALYSIS																				•
STUDY CONCLUSION											•	•				•				•

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● is used to indicate a study procedure that requires documentation in the individual CRF/eCRF; ○ is used to indicate a study procedure that does not require documentation in the individual CRF/eCRF

SCR = Screening; Sft FU = Safety Follow-up; FU = follow-up

\*\* Refer to section [6.8](#).

\*\*\* Local symptoms will be recorded separately for each injection site (i.e. for RTS,S/AS01<sub>E</sub>, *Engerix-B*, *Infanrix/Hib* and *Synflorix*); general symptoms will be recorded for all vaccines

a Study personnel will visit the infants on days 1, 2, 3, 4, 5 and day 6 after each vaccination of RTS,S/AS01<sub>E</sub> or *Engerix-B*.

b Unsolicited symptoms will be recorded for 30 days (day of vaccination and 29 subsequent days) after the first, second and third doses of RTS,S/AS01<sub>E</sub> or *Engerix-B*.

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It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses. The intervals are tabulated in [Table 6](#).

**Table 6 Intervals between study visits**

Interval	Optimal length of interval <sup>1</sup>	Minimum - maximum interval allowed <sup>2</sup>
Clinic Visit 1 (Screening)→ Clinic Visit 2	-	-14–0 days
Clinic Visit 2→ Clinic Visit 3	14 days	7–21 days
Clinic Visit 2→ Clinic Visit 4	28 days	28–42 days
Clinic Visit 4→ Clinic Visit 5	14 days	7–21 days
Clinic Visit 4→ Clinic Visit 6	28 days	28–42 days
Clinic Visit 6→ Clinic Visit 7	14 days	7–21 days
Clinic Visit 6→ Clinic Visit 8	28 days	28–42 days
Clinic Visit 2→ Clinic Visit 9	8 months	7–9 months
Clinic Visit 2→ Clinic Visit 10	14 months	13–15 months
Clinic Visit 2→ Clinic Visit 11	16 months	15–17 months
Clinic Visit 2→ Clinic Visit 12	17 months	16–18 months
Clinic Visit 2→ Clinic Visit 13	26 months	26–27 months
Clinic Visit 2→ Clinic Visit 14	38 months	38–39 months
Clinic Visit 2→ Clinic Visit 15	50 months	50–51 months
Clinic Visit 15→ Clinic Visit 16	28 days	21–42 days

<sup>1</sup> Whenever possible the investigator should arrange study visits within this interval

<sup>2</sup> Subjects will not be eligible for inclusion in the ATP-cohort for analysis if they make the study visit outside this interval

## 5.6. Detailed description of study procedures

### 5.6.1. Procedures prior to study participation

#### 5.6.1.1. Informed consent of pregnant women

Pregnant women will be identified at antenatal clinics or in the community and will be informed about the study. If interested in participating they will be asked to sign a consent form for screening for hepatitis B or HIV infection.

Mothers who were screened negative for HBsAg and HIV and who agree to let their child participate in the study will be invited for the screening visit (Visit 1).

#### 5.6.1.2. Informed consent of infants

Before performing any other study procedure, the signed/thumb-printed informed consent of the subject's parent(s)/LAR(s) needs to be obtained. When the parent(s)/LAR(s) of the child are illiterate, the ICF will also be signed and dated by a literate impartial witness. Refer to Section [5.1](#) for the requirements on how to obtain informed consent, as appropriate.

The parent(s)/LAR(s) of children who have been consented for the study and found to be ineligible will receive a full explanation by a study clinician at a private meeting. Any clinically relevant finding will be treated appropriately by a physician.

## **5.6.2. Procedures prior to the first vaccination**

### **5.6.2.1. Assign subject number**

Subject number to be assigned at the screening visit.

### **5.6.2.2. Collect demographic data**

Record demographic data such as age and gender in the subject's CRF/eCRF.

### **5.6.2.3. Medical history**

Perform a history-directed medical examination and record any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study in the CRF/eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

### **5.6.2.4. Check inclusion and exclusion criteria**

**Check all applicable inclusion and exclusion criteria as described in Sections 4.3 and 4.4 before enrolment.**

### **5.6.2.5. Physical examination**

Discuss with the parent(s)/LAR(s) about the current health of their child and then perform a physical examination of the child. Collected information needs to be recorded in the CRF/eCRF.

### **5.6.2.6. Blood sampling for safety or immune response assessments**

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are to be taken at specific study visits. After centrifugation, serum samples must be kept at – 20°C until shipment. Volumes of blood to be taken are given in Table 7.

Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

## **5.6.3. Procedures during the primary vaccination epoch**

Note that some of the procedures to be performed during the primary epoch are also performed at screening/prior to the first vaccination and are described in Section 5.6.2.

**5.6.3.1. Check and record concomitant medication/vaccination and intercurrent medical conditions**

Concomitant medication/vaccination must be recorded in the CRF/eCRF as described in Section 6.7. Refer also to Section 6.7 for details on the medication/vaccination forbidden and/or allowed during the study.

**At each study visit subsequent to the first vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.8. If it is the case, the condition(s) must be recorded in the CRF/eCRF.**

**5.6.3.2. Check contraindications, warnings and precautions to vaccination**

Contraindications, warnings and precautions to vaccination are to be checked at the beginning of each vaccination visit. Refer to Section 6.5 and 6.6.

**5.6.3.3. Assess pre-vaccination body temperature**

The body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever [fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  on axillary setting, or  $\geq 38.0^{\circ}\text{C}$  on rectal setting] on the day of vaccination, the vaccination visit will be rescheduled within the interval for this visit (see Table 6).

**5.6.3.4. Randomization**

At the first vaccination visit, randomization will occur as explained in Section 5.2.

**5.6.3.5. Vaccine number assignment**

At each vaccination visit, the subject will be assigned a vaccine number defining the treatment he/she will be receiving. The vaccine number must be recorded in the CRF/eCRF at each vaccination visit.

**5.6.3.6. Vaccination**

After completing the prerequisite procedures prior to vaccination, study vaccines will be administered (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit.

The vaccinees will be observed closely for at least 60 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccines.

Vaccination will take place at the vaccination center. All vaccinations will be given by a qualified person: a nurse or a doctor. A staff member experienced in the resuscitation of children will be available at all vaccination sessions.

**5.6.3.7. Recording of non-serious AEs and SAEs**

Refer to Section 8.2 for procedures for the Investigator to record AEs and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.3 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

The subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.

SAEs will be detected through the in-patient and out-patient services in the study area through close cooperation between study personnels performing the home visits and the medical staff at government facilities.

Solicited AEs will be collected for 7 days (day 0 to 6) following the administration of each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines. Study personnels will visit each child after primary vaccination with RTS,S/AS01<sub>E</sub> or *Engerix-B* and record any local and general solicited AEs and unsolicited AEs.

Unsolicited AEs will be collected for 30 days (day 0 to 29) following the administration of each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines.

SAEs will be collected until 8 months after Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. The capture of SAEs will be facilitated by means of clinic visits. During the planned visits, the subject's parent(s)/LAR(s) will be asked retrospectively if any medical event that might be an SAE occurred since the last visit and this information will be recorded. Unreported SAEs detected in this way will be investigated and reported by the PI or delegate on the corresponding SAE screen/SAE form. In the case of a death which has occurred at home, supplementary information will be obtained using the verbal autopsy technique. The verbal autopsy will be conducted according to previously published methods and detailed in the SOPs on file with the investigators [Smith, 1991].

If any child is reported to be unwell at the time of a home visit, the study personnel will advise the parent(s)/LAR(s) to seek care at the vaccination center. In the event that a child is seriously ill, the study personnel will inform the PI or designate, and transport will be arranged, as applicable, to the referral hospital, if judged appropriate by the responsible clinician.

**5.6.3.8. Conclusion of the primary epoch**

A primary analysis will be performed on safety and immunogenicity data collected up to one month following the administration of the third dose of study vaccine (Clinic Visit 8). At the end of the primary vaccination epoch, the investigator is to fill in the study conclusion page of the CRF/eCRF.

**5.6.4. Procedures during follow-up epochs**

Note that some of the procedures to be performed during the follow-up epochs are also performed during the screening epoch and during the primary vaccination epoch and are described in Sections 5.6.2 and 5.6.3.

**5.6.4.1. Study conclusions**

A safety analysis will be performed on data (SAEs) collected up to 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B* (Visit 9). At the end of the Safety follow-up epoch, the investigator is to fill in the study conclusion page of the CRF/eCRF.

An immunogenicity analysis based on data collected until Visit 13 (Month 26) will include anti-CS and anti-HBs antibody responses. At the end of the Immunogenicity follow-up 1 epoch, the investigator is to fill in the study conclusion page of the CRF/eCRF.

A final analysis will be performed on further safety and immunogenicity data collected up to the last study visit (Visit 16), 51 months following the administration of the first dose of study vaccine. At the end of the immunology follow-up 2 epoch, the investigator is to fill in the study conclusion page of the CRF/eCRF.

**5.7. Biological sample handling and analysis**

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccines and its constituents or the disease under study for a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject's parent(s)/LAR(s).

Any human pharmacogenetic testing will require specific consent from the individual subject's parent(s)/LAR(s) and the ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).



If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

#### 5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

#### 5.7.2. Biological samples

Details of the quantity of blood to be taken at each timepoint during the study are provided in Table 7.

**Table 7 Biological samples**

Time point	Subjects	Sample type	Quantity	Unit
Screening Clinic Visit 1 (Day -14 to 0)	All	Blood	3.0	ml
Clinic Visit 8 (Month 3)	REP[Ro]s	Blood	4.8	ml
	RERo[P]s	Blood	2.1	ml
	RE[RoP]s	Blood	1.6	ml
	HEP[Ro]s	Blood	4.8	ml
	HERo[P]s	Blood	2.1	ml
Clinic Visit 10 (Month 14)	All	Blood	0.6	ml
Clinic Visit 12 (Month 17)	REP[Ro]s	Blood	3.2	ml
	HEP[Ro]s	Blood	3.2	ml
Clinic Visit 13 (Month 26)	All	Blood	0.6	ml
Clinic Visit 14 (Month 38)	All	Blood	0.6	ml
Clinic Visit 15 (Month 50)	All	Blood	0.6	ml
Clinic Visit 16 (Month 51)	All	Blood	1.0	ml

**5.7.3. Laboratory assays**

Please refer to [APPENDIX A](#) for a detailed description of the assays performed in the study.

Serological assays for the determination of antibodies against CS, HBs, HBs RF1, 10 pneumococcal vaccine serotypes, protein D, 3 pertussis antigens and rotavirus will be performed by ELISA at a GSK Biologicals' laboratory or in a validated laboratory designated by GSK Biologicals using standardised and validated procedures (refer to [Table 8](#)).

Determination of opsonophagocytic activity against the 10 pneumococcal vaccine serotypes will be conducted at GSK Biologicals' laboratory according to standard methodologies as detailed in the laboratory SOP's (see [APPENDIX A](#)).

**Table 8 Humoral immunity (antibody determination)**

System	Component	Method	Unit	Cut-off	Laboratory
0492.001	Plasmodium falciparum.Circumsporozoite Protein.R32LR Ab.IgG	Enzyme Linked Immuno Sorbent Assay	enzyme linked immunosorbent assay unit per milliliter	0.5	Leroux-Roels Laboratory, CEVAC, Ghent, Belgium
0177.004	Hepatitis B Virus.Surface Ab	Enzyme Linked Immuno Sorbent Assay	milli-international unit per milliliter	10	GSK Bio*, Rixensart
0494.001	Hepatitis B Virus.RF1 Ab	Enzyme Linked Immuno Sorbent Assay	enzyme linked immunosorbent assay unit per milliliter	33	Leroux-Roels Laboratory, CEVAC, Ghent, Belgium
0497.001	Rotavirus Ab.IgA	Enzyme Linked Immuno Sorbent Assay	unit per milliliter	20	GSK Bio*, Rixensart
0486.001	Bordetella pertussis.Pertussis Toxin Ab.IgG	Enzyme Linked Immuno Sorbent Assay †	enzyme linked immunosorbent assay unit per milliliter	5	GSK Bio*, Rixensart
0137.001	Bordetella pertussis.Filamentous Hemagglutinin Ab.IgG	Enzyme Linked Immuno Sorbent Assay †	enzyme linked immunosorbent assay unit per milliliter	5	GSK Bio*, Rixensart
0470.001	Bordetella pertussis.Pertactin Ab.IgG	Enzyme Linked Immuno Sorbent Assay †	enzyme linked immunosorbent assay unit per milliliter	5	GSK Bio*, Rixensart
0393.001	(Non Typeable) Haemophilus influenzae. Protein D Ab. IgG	Enzyme Linked Immuno Sorbent Assay	enzyme linked immunosorbent assay unit per milliliter	100	GSK Bio*, Rixensart
0405.002	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0427.002	Streptococcus pneumoniae.Polysaccharide 04 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0430.002	Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0434.002	Streptococcus pneumoniae.Polysaccharide	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart

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System	Component	Method	Unit	Cut-off	Laboratory
	06B Ab.IgG				
0437.002	Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0442.002	Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0411.002	Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0414.002	Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0418.002	Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0421.002	Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	µg/ml	0.05	GSK Bio*, Rixensart
0449.001	Streptococcus pneumoniae Serotype 01/37 Brugmann Hospital Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0457.001	Streptococcus pneumoniae Serotype 04/2656 Brugmann Hospital Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0458.001	Streptococcus pneumoniae Serotype 05 Ambrose- Statens Serum Institut Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0460.001	Streptococcus pneumoniae Serotype 06B/DS2212/94 Centers for Disease Control Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0461.001	Streptococcus pneumoniae Serotype 07F/46 Brugmann Hospital Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0463.001	Streptococcus pneumoniae Serotype 09V/112 161/95 Statens Serum Institut Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0450.001	Streptococcus pneumoniae Serotype 14/58 Brugmann Hospital Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0451.001	Streptococcus pneumoniae Serotype 18C/4593/40 Statens Serum Institut Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0453.001	Streptococcus pneumoniae Serotype 19F/2737 Brugmann Hospital Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart
0454.001	Streptococcus pneumoniae Serotype 23F Mac-Statens Serum Institut Ab	Opsonophagocytose	1/dilution	8	GSK Bio*, Rixensart

\*GSK Biologicals' (Rixensart, Belgium) central laboratory, or in a validated laboratory designated by GSK Biologicals  
† or a multiplex assay

**Table 9 Hematology, Serum Chemistry**

System	Component	Scale
0692.001	Hemoglobin	Quantitative
0747.001	Leukocytes (White Blood Cells)	Quantitative
0713.001	Platelets	Quantitative
0628.001	Alanine Aminotransferase	Quantitative
0658.001	Creatinine	Quantitative

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (Sponsor-dependent) but laboratory-independent Quality Department.

#### **5.7.4. Biological samples evaluation**

##### **5.7.4.1. Immunological read-outs**

Blood samples will be collected for assessment of serology.

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**Table 10 Summary of blood sampling time points, immunological read-outs and volumes to be collected for infants in treatment group REP[Ro]<sub>s</sub>**

Blood sampling time point			Component	No. subjects	Laboratory	Priority Rank	Volume of whole blood required
Timing	Time point	Visit No.					
Pre Dose 1	screening visit	1	<b>Safety analysis</b>				
			Hemoglobin and total WBC	141	on-site	1	2 ml
			Platelets	141	on-site		
			ALT and Creatinine	141	on-site		
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	2	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or Engerix-B	Month 3	8	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	4	0.2 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (ELISA)	141	GSK Bio*	3	1.5 ml
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (OPA)	141	GSK Bio*	7	1.5 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or Engerix-B (1 year)	Month 14	10	Protein D antibodies	141	GSK Bio*	5	0.2 ml
			anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	6	0.4 ml
			<b>Investigational analysis</b>				
1 month post Booster 1	Month 17	12	Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (ELISA)	141	GSK Bio*	1	1.5 ml
Eight months post Booster 1	Month 26	13	Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (OPA)	141	GSK Bio*	2	1.5 ml
			Protein D antibodies	141	GSK Bio*	3	0.2 ml
			<b>Investigational analysis</b>				
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or Engerix-B (3 years)	Month 38	14	Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or Engerix-B (4 years)	Month 50	15	Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
One month post Booster 2	Month 51	16	Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
			<b>Investigational analysis</b>				

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**Table 11 Summary of blood sampling time points, immunological read-outs and volumes to be collected for infants in treatment group RERo[P]<sub>s</sub>**

Blood sampling time point			Component	No. subjects	Laboratory	Priority Rank	Volume of whole blood required
Timing	Time point	Visit No.					
Pre Dose 1	Screening	1	<b>Safety analysis</b>				
			Hemoglobin and total WBC	141	on-site	1	2 ml
			Platelets	141	on-site		
			ALT and Creatinine	141	on-site		
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	2	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i>	Month 3	8	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	4	0.2 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
			Rotavirus IgA	141	GSK Bio*	3	0.5 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (1 year)	Month 14	10	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	5	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Eight months post Booster 1	Month 26	13	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (3 years)	Month 38	14	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (4 years)	Month 50	15	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
One month post Booster 2	Month 51	16	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml

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**Table 12 Summary of blood sampling time points, immunological read-outs and volumes to be collected for infants in treatment group RE[RoP]<sub>s</sub>**

Blood sampling time point			Component	No. subjects	Laboratory	Priority Rank	Volume of whole blood required
Timing	Time point	Visit No.					
Pre Dose 1	Screening	1	<b>Safety analysis</b>				
			Hemoglobin and total WBC	141	on-site	1	2 ml
			Platelets	141	on-site		
			ALT and Creatinine	141	on-site		
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	2	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i>	Month 3	8	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (1 year)	Month 14	10	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Eight months post Booster 1	Month 26	13	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (3 years)	Month 38	14	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (4 years)	Month 50	15	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
One month post Booster 2	Month 51	16	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml

\* or validated laboratory designated by GSK Biologicals

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**Table 13 Summary of blood sampling time points, immunological read-outs and volumes to be collected for infants in treatment group HEP[Ro]<sub>s</sub>**

Blood sampling time point			Component	No. subjects	Laboratory	Priority Rank	Volume of whole blood required
Timing	Time point	Visit No.					
Pre Dose 1	Screening	1	<b>Safety analysis</b>				
			Hemoglobin and total WBC	141	on-site	1	2 ml
			Platelets	141	on-site		
			ALT and Creatinine	141	on-site		
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	2	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01E or Engerix-B	Month 3	8	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	4	0.2 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (ELISA)	141	GSK Bio*	3	1.5 ml
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (OPA)	141	GSK Bio*	7	1.5 ml
Post Dose 3 of RTS,S/AS01E or Engerix-B (1 year)	Month 14	10	Protein D antibodies	141	GSK Bio*	5	0.2 ml
			anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	6	0.4 ml
			<b>Investigational analysis</b>				
1 month post Booster 1	Month 17	12	Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
Eight months post Booster 1	Month 26	13	Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (ELISA)	141	GSK Bio*	1	1.5 ml
			Pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (OPA)	141	GSK Bio*	2	1.5 ml
			Protein D antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01E or Engerix-B (3 years)	Month 38	14	<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
Post Dose 3 of RTS,S/AS01E or Engerix-B (4 years)	Month 50	15	<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
One month post Booster 2	Month 51	16	<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml

\* or validated laboratory designated by GSK Biologicals



**Table 14 Summary of blood sampling time points, immunological read-outs and volumes to be collected for infants in treatment group HERo[P]<sub>s</sub>**

Blood sampling time point			Component	No. subjects	Laboratory	Priority Rank	Volume of whole blood required
Timing	Time point	Visit No.					
Pre Dose 1	Screening	1	<b>Safety analysis</b>				
			Hemoglobin and total WBC	141	on-site	1	2 ml
			Platelets	141	on-site		
			ALT and Creatinine	141	on-site		
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	2	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	3	0.2 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i>	Month 3	8	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	4	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
			Anti-CS antibodies	141	GSK Bio*	4	0.2 ml
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml
			Rotavirus IgA	141	GSK Bio*	3	0.5 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (1 year)	Month 14	10	anti-acellular B-pertussis antibodies (Anti-PT, anti-FHA and anti-PRN)	141	GSK Bio*	5	0.4 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Eight months post Booster 1	Month 26	13	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (3 years)	Month 38	14	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
Post Dose 3 of RTS,S/AS01 <sub>E</sub> or <i>Engerix-B</i> (4 years)	Month 50	15	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs antibodies	141	GSK Bio*	1	0.4 ml
One month post Booster 2	Month 51	16	Anti-CS antibodies	141	GSK Bio*	2	0.2 ml
			<b>Investigational analysis</b>				
			Anti-HBs RF1 like antibodies	141	GSK Bio*	2	0.6 ml

\* or validated laboratory designated by GSK Biologicals

Additional testing on the immune response to the vaccine antigens may be done if specific validated assays become available in the GSK Biological laboratory or in a validated laboratory designated by GSK Biological's, or if they are deemed necessary based on the results of this study, other studies or medical advancements or for development of new assays regarding the diseases or vaccines under evaluation.

### 5.7.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the CS antigen or for the rotavirus IgA.

For the HBsAg, the conventional correlate of protection is anti-HBs antibody titers above 10 mIU/ml [[European Consensus Group on Hepatitis B Immunity](#), 2000].

At the time this protocol was prepared, a pneumococcal correlate of protection had not been clearly established.

For pertussis antigens, clinical protection has recently been shown to be correlated with the presence of antibodies against pertactin, pertussis toxin and fimbrial agglutinogens 2 and 3. However, no definite serological correlates, i.e., threshold antibody concentrations, of protection have been established to date. Subjects presenting with the following antibody responses after vaccination will be offered an additional dose of an approved vaccine:

- anti-PT antibody concentration < 5 EI.U/ml,
- anti-FHA antibody concentration < 5 EI.U/ml,
- anti-PRN antibody concentration < 5 EI.U/ml.

## **6. STUDY VACCINES AND ADMINISTRATION**

### **6.1. Description of study vaccines**

The Quality Control Standards and Requirements for each candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

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**Table 15 Study vaccines**

Vaccine	Formulation	Presentation	Volume	Number of doses
RTS,S/AS01E	<b>RTS,S antigen:</b> 31.25 µg of RTS,S with 15.75 mg of sucrose as cryoprotectant per 3 ml monodose vial. <b>AS01E adjuvant:</b> 25 µg of MPL and 25 µg QS21 (a triterpene glycoside purified from the bark of <i>Quillaja saponaria</i> ) with liposomes.	<b>RTS,S antigen:</b> Lyophilized pellet in a glass vial. The pellet is reconstituted with adjuvant in liquid form and 0.5 ml of reconstituted vaccine contains 25µg RTS,S. <b>AS01E adjuvant:</b> liquid solution in a monodose glass vial. The reconstituted RTS,S/AS01E vaccine is an opalescent liquid.	0.5 ml	3
Engerix-B	The pediatric dosage vial contains 10 µg of purified major hepatitis B surface antigen adsorbed onto 0.25 mg of Al+++ as aluminium hydroxide.	The content, upon storage, may present a fine white deposit with a clear colourless supernatant. Once shaken, the vaccine is slightly opaque.	0.5 ml	3 + 1 booster
Infanrix/Hib	After reconstitution, 1 dose (0.5 ml) contains: diphtheria toxoid, tetanus toxoid, pertussis antigens (pertussis toxoid, Filamentous Haemagglutinin, Pertactin), Haemophilus influenzae type b polysaccharide and conjugated to tetanus toxoid. The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine components are adsorbed on aluminium salts. The final vaccine is formulated in saline. The excipients of Infanrix/Hib comprise lactose, aluminium hydroxide, sodium chloride and water for injections.	The liquid DTPa component is presented as a turbid white suspension in a pre-filled syringe. The Hib component is supplied as a white freeze-dried pellet in monodose vials to be reconstituted before use with the liquid DTPa component supplied in the pre-filled syringe.	0.5 ml	3 + 1 booster
Polio Sabin	<i>Polio Sabin</i> (OPV MRC5) is a stabilized suspension of types 1, 2 and 3 live attenuated polioviruses (Sabin strains): Type 1 (strain LSc, 2ab), Type 2 (strain P 712 ch, 2ab), Type 3 (strain Leon 12a, 1b). The viruses are propagated in human diploid cells. The excipients of <i>Polio Sabin</i> (oral) comprise magnesium chloride, L-arginine, polysorbate 80, neomycin sulphate (residual), polymyxin B sulphate (residual) and purified water.	Polio Sabin is a stabilized suspension in a glass vial. For the multidose container (WHO formulation), one immunizing dose of 0.1 ml is contained in 2 drops.	0.1 ml (2 drops)	3
Synflorix	Synflorix is a liquid 10-valent conjugate vaccine with protein D and diphtheria and tetanus toxoids as protein carriers. The excipients of Synflorix comprise sodium chloride and water.	It is presented as a turbid white suspension in a pre-filled syringe.	0.5 ml	3 + 1 booster
Rotarix	Rotarix contains not less than 10 <sup>6.0</sup> CCID <sub>50</sub> (Cell Culture Infectious Dose 50%) of live attenuated human rotavirus RIX4414 strain. The excipients of Rotarix (oral) comprise sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM), calcium carbonate, xanthan and sterile water.	It is presented as powder in a glass container and an oral applicator containing the diluent.	<del>1.5</del> 1.0 ml	2

22-NOV-2011  
00094d0d3fadeb685a34b0bd4e19f9cab10c00f4

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13-MAY-2014  
572979f0fc0450209ec8c02e1ea00966f8ea8025

513

**6.1.1. Vaccines given according to local policy**

**6.1.1.1. Measles**

A measles vaccine, either licensed by the FDA or by the EMA and/or prequalified by WHO, will be used to vaccinate the infants. The vaccine that will be used will be sourced locally.

**6.1.1.2. Yellow fever**

Yellow fever vaccine will be given according to local treatment regulations. The vaccine that will be used will be sourced locally.

**6.2. Storage and handling of study vaccines**

The study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorised personnel.

The study vaccines must be stored at the defined temperature range (i.e. +2 to +8°C). Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines. The storage temperature of the vaccines will be monitored daily with temperature monitoring device(s) (at the minimum calibrated) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation outside the range 0 to +8°C must be reported to the sponsor as soon as detected. Following an exposure to a temperature deviation, vaccines will not be used until approval has been given by the Sponsor.

In case of temperature deviation between 0 and +2°C, the impacted study vaccines can still be administered, but the site must take adequate actions to go back to the defined range +2 to +8°C and avoid re-occurrence of such a temperature deviation.

Please refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the Temperature deviation process, packaging and accountability of the study vaccines.

**6.3. Dosage and administration of study vaccines****Table 16 Dosage and administration**

Type of contact and timepoint	Vaccine	Treatment Groups	Route <sup>1</sup>	Site <sup>2</sup>	Side <sup>3</sup>
visit 2 (Day 0)	RTS,S/AS01 <sub>E</sub>	REP[Ro] <sub>s</sub> , RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub>	IM	Ant T	L
	<i>Engerix-B</i>	HEP[Ro] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	L
	<i>Infanrix/Hib</i>	all groups	IM	D	R
	<i>Polio Sabin</i>	all groups	O	-	-
	<i>Synflorix</i>	REP[Ro] <sub>s</sub> , HEP[Ro] <sub>s</sub>	IM	Ant T	R
visit 3 (Day 14)	<i>Synflorix</i>	RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	R
visit 4 (Day 28)	RTS,S/AS01 <sub>E</sub>	REP[Ro] <sub>s</sub> , RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub>	IM	Ant T	L
	<i>Engerix-B</i>	HEP[Ro] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	L
	<i>Infanrix/Hib</i>	all groups	IM	D	R
	<i>Polio Sabin</i>	all groups	O	-	-
	<i>Synflorix</i>	REP[Ro] <sub>s</sub> , HEP[Ro] <sub>s</sub>	IM	Ant T	R
	<i>Rotarix</i>	RERo[P] <sub>s</sub> , HERo[P] <sub>s</sub>	O	-	-
visit 5 (Day 42)	<i>Synflorix</i>	RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	R
	<i>Rotarix</i>	REP[Ro] <sub>s</sub> , RE[RoP] <sub>s</sub> , HEP[Ro] <sub>s</sub>	O	-	-
visit 6 (Day 56)	RTS,S/AS01 <sub>E</sub>	REP[Ro] <sub>s</sub> , RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub>	IM	Ant T	L
	<i>Engerix-B</i>	HEP[Ro] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	L
	<i>Infanrix/Hib</i>	all groups	IM	D	R
	<i>Polio Sabin</i>	all groups	O	-	-
	<i>Synflorix</i>	REP[Ro] <sub>s</sub> , HEP[Ro] <sub>s</sub>	IM	Ant T	R
	<i>Rotarix</i>	RERo[P] <sub>s</sub> , HERo[P] <sub>s</sub>	O	-	-
visit 7 (Day 70)	<i>Synflorix</i>	RERo[P] <sub>s</sub> , RE[RoP] <sub>s</sub> , HERo[P] <sub>s</sub>	IM	Ant T	R
	<i>Rotarix</i>	REP[Ro] <sub>s</sub> , RE[RoP] <sub>s</sub> , HEP[Ro] <sub>s</sub>	O	-	-
visit 9 (Month 8)	Measles	all groups	IM	D	-
	Yellow fever	all groups	IM	D	-
visit 11 (Month 16)	<i>Infanrix/Hib</i>	all groups	IM	D	R
	<i>Synflorix</i>	all groups	IM	Ant T	R
visit 15 (Month 50)	<i>Engerix-B</i>	all groups	IM	Ant T	L

<sup>1</sup>Oral (O)/ Intramuscular (IM)<sup>2</sup>Deltoid (D); Ant T = Anterolateral thigh<sup>3</sup>Left (L)/ Right (R)

The vaccinees will be observed closely for at least 60 minutes following the administration of all vaccines used in the study, with appropriate medical treatment readily available in case of an anaphylactic reaction.

**6.3.1. RTS,S/AS01<sub>E</sub> (0.5 ml dose)**

RTS,S/AS01<sub>E</sub> will be supplied such that the reconstituted vaccine volume will provide a 0.5 ml pediatric dose. One 0.5 ml dose will be withdrawn from each vial and used.

Disinfect top of vaccine vial (pellet) and adjuvant vial with alcohol swabs and let dry. Withdraw the contents of the adjuvant vial in a syringe and inject adjuvant into the vial of lyophilized antigen. The pellet is then dissolved by gently shaking the vial. Wait for 1 minute to ensure complete dissolution of vial contents before withdrawing the content of the vial (0.5 ml). The reconstituted vaccine should be administered by slow IM injection, using a fresh 25G needle with length of 1 inch (25 mm): for children 8 to 12 weeks of age at enrolment inject into the left antero lateral thigh for primary course. Vaccine should be injected within 4 hours of reconstitution (storage at +2°C to +8°C).

### 6.3.2. *Engerix-B* (0.5 ml dose)

Disinfect the top of the vaccine vial with alcohol swabs and shake gently while letting the alcohol dry. Then withdraw the contents of the vial into a syringe for injection using a fresh syringe and needle. Remove and discard the needle using appropriate safety precautions. Use a fresh needle for injection. The vaccine should be administered soon afterwards intramuscularly in the left antero-lateral thigh, using a 25G needle with length of 1 inch (25 mm) (storage at 2°C to 8°C). Children of both groups should be injected in the left antero-lateral thigh with *Engerix-B* as booster.

### 6.3.3. *Polio Sabin*

The OPV vaccine will be administered orally. For the multidose container (WHO formulation), one immunizing dose of 0.1 ml is contained in 2 drops.

After opening, multidose containers should be kept in a refrigerator and used within eight hours.

### 6.3.4. *Infanrix/Hib* (0.5 ml dose)

One dose of the GSK Biologicals' *Infanrix*<sup>TM</sup> vaccine will be used to reconstitute one dose of the Hib vaccine as follows: The Hib vial should be taken out of the refrigerator 5 minutes before reconstitution. The liquid *Infanrix* vaccine should always be shaken before use. Cleanse the rubber stopper of the Hib conjugate vaccine with a suitable germicide and inject the entire volume of the *Infanrix* pre-filled syringe into the vial of lyophilized Hib. The vial must be shaken well until the lyophilized Hib vaccine pellet has completely dissolved. After reconstitution, withdraw the reconstituted vaccine (0.5 ml). Remove and discard the needle used for reconstitution and replace it with a new needle to administer the vaccine. The vaccine must be used immediately after reconstitution. When reconstituted with Hib, the liquid *Infanrix* may appear as a slightly more cloudy suspension than the liquid components alone. In the event of other variations being observed, the vaccine should be discarded.

In order to ensure proper intramuscular injection of the study vaccines, a needle of at least 1 inch (2.54 cm) length, 25 gauge will be used. The vaccine will be administered as an intramuscular injection into the ~~left~~ **right** deltoid.

**6.3.5. Rotarix (4-5 1.0 ml dose)**

To prepare the vaccine for administration, the entire content of one pre-filled oral applicator containing the liquid for reconstitution should be transferred into the vial of the lyophilized product (vaccine) by using the transfer adaptor. The vial should be shaken well to resuspend the vaccine. The entire volume of the resuspended product should be withdrawn into the same oral applicator, the transfer adaptor should be discarded and the resuspended product should then be administered smoothly as a single oral dose.

**6.3.6. Synflorix (0.5 ml dose)**

The syringe containing the liquid pneumococcal vaccine (10Pn-PD-DiT conjugate vaccine or *Synflorix*) must be shaken before use to obtain a homogeneous whitish suspension. One dose of 0.5 ml of the vaccine will be injected intramuscularly into the right anterolateral thigh. The vaccine should be administered by slow IM injection.

**6.3.7. Measles**

The measles vaccine will be used according to manufacturer instructions and the Summary of Product Characteristics. The vaccine will be administered as an intramuscular injection into the deltoid.

**6.3.8. Yellow fever**

The yellow fever vaccine will be used according to manufacturer instructions and the Summary of Product Characteristics. The vaccine will be administered as an intramuscular injection into the deltoid.

**6.4. Replacement of unusable vaccine doses**

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects, at least 5% additional doses will be supplied to replace those that are unusable.

**6.5. Contraindications to subsequent vaccination****6.5.1. Absolute contraindications to further vaccination**

The following events constitute absolute contraindications to further administration of study vaccines. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.3.4).

- Acute allergic reaction, significant IgE-mediated event or anaphylactic shock following the administration vaccines.

- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- Failure to thrive.
- Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.

### 6.5.2. Indications for deferral of vaccination

The following events constitute contraindications to administration of study vaccines at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 8.3.4).

- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature  $\geq 37.5^{\circ}\text{C}$  on oral, axillary or tympanic setting, or  $\geq 38.0^{\circ}\text{C}$  on rectal setting.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- A lesion that would prevent intramuscular injection
- Administration of a vaccine not foreseen by the study protocol within 7 days of any dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* vaccine.

### 6.6. Warnings and precautions

Refer to the approved product label/package insert or in the Summary of Product Characteristics.

### 6.7. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject's parent(s)/LAR(s) about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, are to be recorded in the CRF/eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring).



Similarly, concomitant medication administered for the treatment of a SAE, at any time, must be recorded on the SAE Report / SAE screens in the eCRF, as applicable. Refer to Section 8.1.2 for the definition of an SAE.

#### **6.7.1. Medications/products that may lead to the elimination of a subject from ATP analyses**

The following criteria should be checked at each visit subsequent to the first vaccination. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Use of a drug or vaccine that is not approved for that indication (by one of the following authorities: FDA or EU member state or WHO [with respect to prequalification]) other than the study vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone  $\geq 0.5$  mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of a licensed vaccine (i.e. a vaccine that is approved by one of the following authorities: FDA or EU member state or WHO [with respect to prequalification]) not foreseen by the study protocol within 7 days of any dose of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- Administration of immunoglobulins and/or any blood products during the study period.

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

#### **6.7.2. Time window for recording concomitant medication/vaccination in the CRF/eCRF**

All antipyretics, analgesics, anti-inflammatories and systemic antibiotics administered in the 7-day period (day of vaccination and 6 subsequent days) following each vaccine dose (i.e. time period for assessment of reactogenicity) will be recorded. The indication for administration ('prophylaxis' or 'treatment') will be recorded (Table 17).

Any licensed vaccine (i.e. a vaccine that is approved by one of the following authorities: FDA or EU member state or WHO [with respect to prequalification]) not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine and ending 30 days after each dose of study vaccine is to be recorded in the eCRF.

Any investigational medication or vaccine (i.e. drug or vaccine that is not approved for that indication by one of the following authorities: FDA or EU member state or WHO [with respect to prequalification]) administered throughout the study (i.e. from Day 0 through Month 51) must be recorded in the eCRF.

Any immunosuppressants or other immune-modifying drugs, any immunoglobulins and/or any blood products administered throughout the study (i.e. from Day 0 through Month 51) must be recorded in the eCRF.

**Table 17 Time window for recording concomitant medication/vaccination**

Time period	Medication/vaccine	Recording period
Primary epoch	Investigational drug or vaccine, immunosuppressants and other immune-modifying drugs, immunoglobulins and blood products	Throughout
	Antipyretics, analgesics, anti-inflammatories, systemic antibiotics	Day of vaccination and 6 subsequent days
	Concomitant vaccination (Licensed vaccine not foreseen in the study protocol)	30 days before and 30 days after each dose of study vaccine
Follow-up epochs	Investigational drug or vaccine, immunosuppressants and other immune-modifying drugs, immunoglobulins and blood products	Throughout

## 6.8. Intercurrent medical conditions that may lead to elimination from an ATP cohort

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an immunodeficiency condition.

## 7. HEALTH ECONOMICS

Not applicable.

## 8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

### 8.1. Safety definitions

#### 8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with

the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

**Examples of an AE include:**

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.

**Examples of an AE DO NOT include:**

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- For therapeutic studies, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

NB AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the CRF/eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

**8.1.2. Definition of a serious adverse event**

A serious adverse event (SAE) is any untoward medical occurrence that:

- a. Results in death.
- b. Is life-threatening.

NB: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- c. Requires hospitalisation or prolongation of existing hospitalisation.

NB: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

- d. Results in disability/incapacity.

NB: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- e. Adverse event of specific interest

NB: AEs of specific interest include **all seizures occurring within a 30-day period of vaccination and immune-mediated disorders**. Key information pertaining to seizures occurring within 7 days of vaccination will be documented in the CRF/eCRF [refer to [Bonhoeffer](#), 2004]. AEs of specific interest to be reported as SAEs also include specific auto-immune diseases and other immune mediated disorders as listed in section [8.2.2.5](#).

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias.

**8.1.3. Solicited adverse events**

The following local (injection-site) AEs will be considered as solicited:

**Table 18 Solicited local adverse events**

Pain at injection site
Redness* at injection site
Swelling at injection site

\* In case the principal investigator or designate is unable to determine the extend of redness on darkly pigmented skin, it will be reported as uninterpretable in the eCRF and Diary Card.

The following general AEs will be considered as solicited:

**Table 19 Solicited general adverse events**

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

NB Temperature will be recorded daily. Should additional temperature measurements be performed, the highest temperature will be recorded in the CRF/eCRF.

Each infant will be observed for at least 60 minutes after vaccination to evaluate and treat any acute adverse events.

After each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines, trained study personnels will visit the children to detect adverse events (AEs) occurring after vaccination for one week (days 1, 2, 3, 4, 5 and day 6 after each vaccination). Thermometers will be provided by the study personnels performing the home visit to record axillary temperature and any local (at the injection site) or general adverse events.

**8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events**

Abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

## 8.2. Detecting and recording adverse events and serious adverse events

### 8.2.1. Time period for detecting and recording adverse events, serious

All AEs starting within 30 days following administration of each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines must be recorded onto/into the AE form/screen in the subject's CRF/eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 8 months following administration of the first dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* for each subject. See Section 8.3 for instructions on reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 20.

**Table 20 Reporting periods for adverse events and serious adverse events**

Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study day	-14 to 0	0	1-6	14	28	29-34	42	56	57-62	70						
Reporting of solicited local and general AEs																
Reporting of unsolicited AEs																
Reporting of SAEs																
Reporting of SAEs related to study participation or any fatal SAE																
Reporting of new onset/worsening of AE of specific interest																

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 20. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

## **8.2.2. Evaluation of adverse events and serious adverse events**

### **8.2.2.1. Active questioning to detect adverse events and serious adverse events**

As a consistent method of detecting soliciting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

*'Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?'*

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF/eCRF or SAE Report Form/screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE pages/SAE screens in the CRF/eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

### **8.2.2.2. Assessment of adverse events**

#### **8.2.2.2.1. Assessment of intensity**

Intensity of the following AEs will be assessed as described:

**Table 21 Intensity scales for solicited symptoms in infants/toddlers and children less than 6 years of age**

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness* at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever**		Record temperature in °C
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

\* In case the principal investigator or designate is unable to determine the extend of redness on darkly pigmented skin, it will be reported as uninterpretable in the eCRF and Diary Card.

\*\* Fever is defined as: rectal temperature  $\geq 38^{\circ}\text{C}$  /axillary temperature  $\geq 37.5^{\circ}\text{C}$  /oral temperature  $\geq 37.5^{\circ}\text{C}$  /tympanic temperature on oral setting  $\geq 37.5^{\circ}\text{C}$ , tympanic temperature on rectal setting  $\geq 38^{\circ}\text{C}$ . The preferred route for recording temperature in this study will be axillary.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0	:	None
1	:	< 5 mm
2	:	5 to 20 mm
3	:	> 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0	:	< 37.5°C
1	:	37.5 – 38.0°C
2	:	> 38 – 39.0°C
3	:	> 39.0°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.



The intensity of each AE and SAE recorded in the CRF/eCRF or SAE Report Form/screens, as applicable, should be assigned to one of the following categories:

- 1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- 2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.
- 3 (severe) = An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at day-care center and would cause the parent(s)/LAR(s) to seek medical advice.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

#### **8.2.2.2.2. Assessment of causality**

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure or Product Information for marketed products in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

*Is there a reasonable possibility that the AE may have been caused by the investigational product?*

- NO : The AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.
- YES : There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (see Section 8.1.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

#### **8.2.2.3. Assessment of outcomes**

Outcome of any non-serious AE occurring within 30 days following administration of each dose of RTS,S/AS01<sub>E</sub> or *Engerix-B* co-administered with EPI vaccines (i.e. unsolicited AE) or any SAE reported during the entire study will be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

#### **8.2.2.4. Medically attended visits**

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the CRF/eCRF.

**8.2.2.5. AEs of specific interest**

Adverse events of specific interest for safety monitoring include seizures within 30 days of vaccination and immune-mediated disorders (IMDs), rashes and mucocutaneous lesions. Support for specific laboratory testing of IMDs and histopathology will be made available by the sponsor.

***Seizures within 30 days of vaccination***

All seizures occurring within a 30-day period of vaccination will be reported as SAEs and medical documentation of the events will be reported in appropriate targeted follow-up forms included in the CRF/eCRF. Key information pertaining to seizures occurring within 7 days of vaccination will be documented in the CRF/eCRF [refer to [Bonhoeffer, 2004](#)].

***Immune-mediated disorders (IMDs)***

Occurrence of IMDs such as those listed below will be reported for all subjects over the entire study period. Medical documentation of the events will be reported in appropriate targeted follow-up forms included in the CRF/eCRF. The specific interest in the detailed description of occurrence of IMDs results from the theoretical concern that vaccination may interfere with immunological self-tolerance. These IMDs will be reported as SAEs in the CRF/eCRF.

- Neuroinflammatory disorders: Optic neuritis, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barré syndrome, myasthenia gravis, encephalitis, neuritis, Bell's palsy.
- Musculoskeletal disorders: Systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, juvenile arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, undifferentiated spondyloarthropathy.
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis, ulcerative proctitis, celiac disease.
- Metabolic diseases: Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, Diabetes Mellitus Type 1, Addison's disease.
- Skin disorders: Psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases.
- Others: Auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, antiphospholipid syndrome, vasculitis, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune myocarditis, sarcoidosis, Stevens-Johnson syndrome.

**8.2.2.6. Rashes and mucocutaneous lesions**

Occurrence of rashes and mucocutaneous lesions that occur within 30 days of vaccination will be reported as AEs/SAEs. Medical documentation of the events will be reported in the CRF/eCRF. Rashes and mucocutaneous lesions that meet the criteria for an SAE are reported in all subjects throughout the study period as usual.

**8.3. Reporting and follow-up of adverse events and serious adverse events****8.3.1. Prompt reporting of serious adverse events and other events to GSK Biologicals**

SAEs will be reported promptly to GSK as described in [Table 22](#) once the investigator determines that the event meets the protocol definition of an SAE.

**Table 22 Time frames for submitting SAEs and other events reports to GSK Biologicals**

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours*	SAE report/SAE screen	24 hours*	SAE report/SAE screen

\* Time frame allowed after receipt or awareness of the information.

In case the electronic reporting system is temporarily unavailable, a back-up system is in place. Please refer to [Section 8.3.3](#) for a detailed description

Study Contact for Reporting SAEs	
<i>Please see the Sponsor Information Sheet for contact details of who to contact in the event of an SAE.</i>	
Back-up Study Contact for Reporting SAEs	
<p align="center"><b>GSK Biologicals Clinical Safety &amp; Pharmacovigilance</b>  Fax: PPD or PPD  24/24 hour and 7/7 day availability  Back-up e-mail if fax is not working: PPD</p>	

**8.3.2. Regulatory reporting requirements for serious adverse events**

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in [Section 8.3.1](#). GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

### **8.3.3. Completion and transmission of SAEs reports to GSK Biologicals**

#### **8.3.3.1. Studies using the paper CRF**

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional relevant information is received and forwarded to GSK WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

Facsimile (Fax) transmission of the SAE Report Form is the preferred method to transmit this information to the Study Contact for Reporting SAEs. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours.

In the event of a death determined by the investigator to be related to vaccination, sending of the fax must be accompanied by telephone call to the Study Contact for Reporting SAEs.

#### **8.3.3.2. Studies using RDE**

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

***Back-up system in case the electronic SAE reporting system does not work***

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.3.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if the back-up system needs to be used).

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if the electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

**8.3.4. Follow-up of adverse events and serious adverse events**

After the initial AE/SAE report, the investigator is required to proactively follow-up each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Investigators will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- Or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

Support for specific laboratory testing of IMDs and histopathology will be made available by the sponsor.

#### **8.4. Treatment of adverse events**

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's CRF/eCRF. Refer to Section 6.7.

#### **8.5. Unblinding**

Not applicable.

#### **8.6. Emergency unblinding**

This study will be open-label, i.e. both the investigator and the subject's parent(s)/LAR(s) will be aware of the vaccine being administered to the subjects. Therefore, the information given hereunder is limited to the unblinding of SAEs to any third parties (e.g. any doctor other than the study investigator), in accordance with GSK Biologicals' standard operating procedures.

The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will in turn contact the GSK Central Safety Physician.

The investigator, or person designated by the investigator, should contact GSK Biologicals' Central Safety physician directly or via the local safety contact (see below

and Study Contact for Emergency Code Break in the Sponsor Information page) to discuss the need for emergency unblinding.

An investigator should request unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccine(s)/product(s) is essential for the clinical management or welfare of the subject.

The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s)/product(s).

<b>GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)</b>
<b>Phones for 7/7 day availability:</b>
PPD [REDACTED] (GSK Biologicals Central Safety Physician on-call)
<b>Back-up phone contact (all countries):</b>
PPD [REDACTED]

## 8.7. Subject card

Study subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject's parent(s)/LAR(s). The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects' parent(s)/LAR(s) must be instructed to keep these cards in their possession at all times.

## 9. SUBJECT COMPLETION AND WITHDRAWAL

### 9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.



## **9.2. Subject withdrawal**

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (see Section 8.3).

Withdrawals will not be replaced.

### **9.2.1. Subject withdrawal from the study**

From an analysis perspective, a ‘withdrawal’ from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a ‘withdrawal’ from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the CRF/eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject’s parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Death
- Other (specify).

### **9.2.2. Subject withdrawal from investigational vaccine**

A ‘withdrawal’ from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration page/screen of the CRF/eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made the subject's parent(s) or LAR(s), by or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Other (specify).

## 10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

### 10.1. Primary endpoint: immunogenicity

- Non-inferiority of the immune response to the hepatitis B antigen induced by RTS,S/AS01<sub>E</sub> vaccine versus a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.

### 10.2. Secondary endpoints

#### *Immunogenicity*

- Non-inferiority of the immune response to the 10 pneumococcal serotype antigens when pneumococcal conjugate vaccine is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response to the 10 pneumococcal serotype antigens of the pneumococcal conjugate vaccine, when given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
  - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response against the protein D (PD) component of the pneumococcal antigen.
  - Anti-PD antibody titers one month post Dose 3 of pneumococcal conjugate vaccine.
- Non-inferiority of the immune response to the rotavirus antigen when the rotavirus vaccine is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.

- Anti-rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.
- Immune response to the rotavirus antigen of the rotavirus vaccine, when given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.
- Immune response to hepatitis B antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
  - Anti-HBs RF1 like antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- Immune response to the CS antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> when given as part of an EPI regimen with and without pneumococcal conjugate vaccine co-administration.
  - Anti-CS antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Immune response to the CS antigen of the investigational vaccine RTS,S/AS01<sub>E</sub> when given as part of an EPI regimen with and without rotavirus co-administration.
  - Anti-CS antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Lot-to lot consistency for immunogenicity of three lots of the investigational vaccine RTS,S/AS01<sub>E</sub>.
  - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Non-inferiority of the immune response to the acellular B pertussis antigens of the DTPa/Hib vaccine when given with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti-acellular B pertussis (BPT) antibody titers (anti-PT, anti-FHA, anti-PRN) at screening and one month post Dose 3 of the DTPa/Hib vaccine.
- Immune response to the acellular B pertussis antigens of the DTPa/Hib vaccine (anti-PT, anti-FHA, anti-PRN) when given with RTS,S/AS01<sub>E</sub>.
  - Anti-acellular B-Pertussis (BPT) antibody titers (anti-PT, anti-FHA, anti-PRN) at screening and one month post Dose 3 of the DTPa/Hib vaccine.

#### ***Immunogenicity follow-up***

- Immune response (on a long-term) to the hepatitis B antigen after a primary course of investigational vaccine RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers assessed at 12, 24, 36 and 48 months post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*.
- Immune response to a booster dose of a licensed hepatitis B vaccine.
  - Anti-HBs antibody titers one month post booster dose of *Engerix-B*.

- Anti-HBs RF1 like antibody titers one month post booster dose of *Engerix-B*.
- Immune response (on a long-term) to the CS-antigen after a primary course of the investigational vaccine RTS,S/AS01<sub>E</sub>.
  - Anti-CS antibody titers assessed 12, 24, 36 and 48 months post Dose 3 of RTS,S/AS01<sub>E</sub>.
- Immune response to a booster dose of pneumococcal conjugate vaccine when primary vaccination is given as part of an EPI regimen with and without RTS,S/AS01<sub>E</sub> co-administration.
  - Anti- pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post booster dose of pneumococcal conjugate vaccine.
  - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post booster dose of pneumococcal conjugate vaccine.
  - Anti-protein D antibody titers one month post booster dose of pneumococcal conjugate vaccine.

### ***Safety***

- For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro]<sub>s</sub>, RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub>, HEP[Ro]<sub>s</sub> and HERo[P]<sub>s</sub>), to describe the occurrence of solicited general and local adverse events (AEs) over a 7-day follow-up period (day of vaccination and 6 subsequent days) after the first, second and third doses of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
- For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro]<sub>s</sub>, RERo[P]<sub>s</sub>, RE[RoP]<sub>s</sub>, HEP[Ro]<sub>s</sub> and HERo[P]<sub>s</sub>), to describe the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after the first, second and third doses of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
- To describe the occurrence of serious adverse events (SAEs).
  - SAEs from the time of first vaccination until 3 month post Dose 1 (Visit 8) of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - SAEs from the time of first vaccination until 8 month post Dose 1 (Visit 9) of RTS,S/AS01<sub>E</sub> or a licensed hepatitis B vaccine.
  - Fatal SAEs from study start until study end.
  - Immune mediated disorders (IMDs) from study start until study end.

### **10.3. Estimated sample size**

A total of 705 subjects (141 per treatment group) are planned to be enrolled in order to have at least 600 evaluable subjects (approximately 120 subjects in each treatment group).

For the primary endpoint, defined as non-inferiority of the anti-HBs seroprotection rate, the study has 92% power to detect an upper limit of the 95% CI on the difference in seroprotection rates (HEP[Ro]<sub>s</sub> + HERo[P]<sub>s</sub> groups minus REP[Ro]<sub>s</sub> + RERo[Po]<sub>s</sub> + RE[RoP]<sub>s</sub> groups) below 5%, with a sample size of 120 evaluable subjects per treatment group (standardized asymptotic 95%; 1-sided alpha 0.025) under the assumption of post vaccination anti-HBs seroprotection rates above 97%. In order to account for drop-out and non-evaluable subjects 141 subjects per treatment group will be enrolled.

For each secondary non-inferiority endpoint, the power for each individual test to demonstrate the following is presented in [Table 23](#):

- non-inferiority of REP[Ro]<sub>s</sub> versus HEP[Ro]<sub>s</sub> in terms of anti PCV response to each of the pneumococcal 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F;
- non-inferiority of RERo[P]<sub>s</sub> versus HERo[P]<sub>s</sub> in terms of anti-rotavirus;

**Table 23 Power for secondary non-inferiority endpoints**

Endpoint	Reference value (Log SD)	Limit of non-inferiority	Power
<i>Synflorix</i> [10PN-PD-DIT-001, <a href="#">GSK data on file 2007</a> ; <a href="#">Vesikari 2009</a> ]			
Anti-4	0.36	2-fold	99%
Anti-6B	0.7	2-fold	91%
Anti-9V	0.4	2-fold	99%
Anti-14	0.39	2-fold	99%
Anti-18C	0.46	2-fold	99%
Anti-19F	0.54	2-fold	99%
Anti-23F	0.43	2-fold	99%
Anti-1	0.36	2-fold	99%
Anti-5	0.35	2-fold	99%
Anti-7F	0.35	2-fold	99%
<i>Rotarix</i> [ROTA-037, <a href="#">GSK data on file 2009</a> ; <a href="#">Madhi 2010</a> ]*			
Anti-RV	0.8	2-fold	83%

Non-inferiority test, alpha (1 sided) = 0.025, N= in each group, power under the alternative of equal proportions/means in both groups, PASS 2005, equivalence of proportions/means

\* This study was conducted at multiple sites in South Africa and Malawi.

For the secondary anti-HBs lot-to-lot consistency endpoint, the trial has 80% power to demonstrate equivalence in terms of anti-HBs response for each GMT ratio between any 2 lots with a log standard deviation not exceeding 0.8 and an equivalence limit of [0.5, 2].

## 10.4. Study cohorts to be evaluated

### 10.4.1. Total vaccinated cohort (TVC)

The TVC will include all vaccinated subjects for whom data are available. Thus, the total analysis of safety will include all subjects with at least one vaccine administration documented and the total analysis of immunogenicity will include vaccinated subjects for

whom data concerning immunogenicity endpoint measures are available. The TVC analysis will be performed per treatment actually administered.

#### 10.4.2. According-To-Protocol (ATP) cohort for analysis of safety

The ATP cohort for analysis of safety will include all vaccinated and eligible subjects

- Who have received at least one dose of study vaccine according to their random assignment.
- For whom administration site of study vaccine is known.
- Who have not received a vaccine not specified or forbidden in the protocol.

#### 10.4.3. According-to-protocol (ATP) cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. The maximum intervals between study visits allowed for inclusion in the ATP analysis are described in [Table 6](#).

### 10.5. Derived and transformed data

#### *Immunogenicity*

- A subject seropositive for anti-CS antibody is a subject whose antibody titer is greater than or equal to the cut-off value (anti-CS  $\geq$  0.5 EU/ml).
- A subject seropositive for anti- RF1 antibody is a subject whose antibody titer is greater than or equal to the cut-off value (anti-CS  $\geq$  33 EU/ml).
- Seroprotection rate for Rotavirus IgA is defined as the percentage of subjects with antibody titers greater than or equal to an established cut-off (anti-rotavirus IgA  $\geq$  20 U/ml).
- Seroprotection rate for HBsAg is defined as the percentage of subjects with antibody titers greater than or equal to an established cut-off (anti-HBs  $\geq$  10 mIU/ml).
- A subject seropositive for 10 pneumococcal vaccine serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) is a subject whose antibody titer is greater than or equal to the cut-off value (pneumococcal serotype specific total IgG  $\geq$  0.05  $\mu$ g/ml).
- A subject seropositive for 10 pneumococcal vaccine serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) is a subject where the opsonic titer able to sustain 50 % killing of live pneumococci under the assay conditions is greater than or equal to the cut-off value (opsonic dilution  $\geq$  8).
- A subject seropositive for pneumococcal conjugate vaccine is defines as a subject whose anti-PD antibody concentrations  $\geq$ 100 EU/ml.

- A subject seropositive for anti-PT, anti-FHA and anti-PRN is defined as a subject whose antibody concentration  $\geq 5$  EL.U/mL. Vaccine response to anti-PT, anti-FHA and anti-PRN is defined as seroconversion in initially seronegative subjects (prior to vaccination) or a concentration post vaccination at least equal to the concentration prior to vaccination in initially seropositive subjects.
- The Geometric Mean Titers/Concentrations (GMTs/GMCs) calculations are performed by taking the anti-log of the mean of the log titer/concentration transformations. Antibody titers/concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

### ***Reactogenicity and Safety***

- Handling of missing data: subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
- For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the total vaccinated cohort will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).

## **10.6. Conduct of analyses**

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

### **10.6.1. Sequence of analyses**

- The primary analysis will be performed on data collected up to Visit 8 (1 month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*) and will include primary and secondary immunogenicity and safety endpoints. Results will be reported in a final study report.
- A safety analysis will be performed on data (SAEs) collected until 8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B* (Visit 9) and will be reported in an annex report.
- An immunogenicity analysis based on data collected until Visit 13 (Month 26) will include anti-CS and anti-HBs antibody responses and will be reported in an annex report.
- The final analysis will be performed on further safety and immunogenicity data collected up to the last study visit (Visit 16), 51 months following the administration of the first dose of study vaccine. Results will be presented in an annex report.

**10.6.2. Statistical considerations for interim analyses**

No interim analysis is planned before the primary analysis.

**10.7. Statistical methods****10.7.1. Analysis of demographics/baseline characteristics**

Demographic characteristics (age and gender) will be tabulated by group.

**10.7.2. Analysis of immunogenicity**

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. A second analysis based on the TVC will be performed to complement the ATP analysis.

**10.7.2.1. Statistical analysis for primary endpoint**

For the primary endpoint, defined as non-inferiority of the anti-HBs seroprotection rate, the difference in percent SP between *Engerix-B* vaccine recipients minus RTS,S/AS01<sub>E</sub> vaccine recipients (HEP[Ro]<sub>s</sub> + HERo[P]<sub>s</sub> groups minus REP[Ro]<sub>s</sub> + RERo[Po]<sub>s</sub> + RE[RoP]<sub>s</sub> groups), assessed one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B* will be calculated as well as the 95% CI (standardized asymptotic) around this difference. If the upper limit of the two-sided 95% CI is below 5%, non-inferiority will have been demonstrated in terms of anti-HBs responses.

**10.7.2.2. Statistical analyses for secondary endpoints****10.7.2.2.1. Analysis of immunogenicity**

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. A second analysis based on the TVC will be performed to complement the ATP analysis.

***Antibodies against Pneumococcal conjugate vaccine (PCV)***

The percentage of subjects with seropositive levels of anti-PCV with 95% CI will be determined at each blood sampling time point for the groups REP[Ro]<sub>s</sub> and HEP[Ro]<sub>s</sub>: that is the proportion of subjects with anti-PCV -1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F - antibody titers as determined by GSK assay greater than or equal to 0.2 µg/ml, which correlates with the standard ELISA value of 0.35 µg/ml. Antibody titers will be summarized by GMC with 95% CI at all time points at which serological samples are taken. Antibody titers after the third dose will also be investigated using reverse cumulative curves. The same analysis will be repeated on data resulting from a quantitative opsonophagocytic assay (95% CIs for the OPA GMT ratios).

The 95% CI of the GMC ratio (HEP[Ro]<sub>s</sub> over REP[Ro]<sub>s</sub>) will be calculated for each of the 10 serotypes (ELISA) one month post Dose 3 of pneumococcal conjugate vaccine. If the upper limit of this CI is below 2, non-inferiority will be concluded.



***Antibodies against Rotavirus Vaccine (RV)***

The percentage of subjects with seropositive levels of anti-RV (proportion of subjects with anti-RV antibody titers as determined by ELISA greater than or equal to 20 U/ml) with 95% CI will be determined at each blood sampling time point for the groups RERo[P]<sub>s</sub> and HERo[P]<sub>s</sub>. Antibody titers will be summarized by GMT with 95% CI at all time points at which serological samples are taken. Antibody titers after the third dose will also be investigated using reverse cumulative curves (RCC).

The 95% CI of the GMT ratio (HERo[P]<sub>s</sub> over RERo[P]<sub>s</sub>) will be calculated one month post Dose 2 of rotavirus vaccine. If the upper limit of this CI is below 2, non-inferiority will be concluded.

***Antibodies against HB***

The seroprotective level for anti-HBs is  $\geq 10$  mIU/ml. The percentage of subjects with protective levels of anti-HBs ( $\geq 10$  mIU/ml) with 95% confidence interval (95% CI) will be determined at each blood sampling time point (all groups). Antibody titers will be summarized by GMT with 95% CI at all time points at which serological samples are taken. Antibody titers after the third dose will also be investigated using RCC.

The 95% CI of the GMT ratio (Lot1/Lot2, Lot2/Lot3 and Lot1/Lot3 within the pooled REP[Ro]<sub>s</sub>, RERo[P]<sub>s</sub> and RE[RoP]<sub>s</sub> groups) will be calculated one month post Dose 3 of RTS,S/AS01<sub>E</sub> or *Engerix-B*. If the CIs are within [0.5, 2], consistency will be concluded.

***Antibodies against RF1***

The percentage of subjects with seropositive levels of anti-RF1 (proportion of subjects with anti-RF1 antibody titers greater than or equal to 33 EU/ml ) with 95% CI will be determined at each blood sampling time point (all groups). Antibody titers will be summarized by GMT with 95% CI at all time points at which serological samples are taken. Antibody titers after the third dose will also be investigated using RCC.

***Antibodies against CS***

The percentage of subjects with seropositive levels of anti-CS (proportion of subjects with anti-CS antibody titers greater than or equal to 0.5 EU/ml ) with 95% CI will be determined at each blood sampling time point (all groups). Antibody titers will be summarized by GMT with 95% CI at all time points at which serological samples are taken. Antibody titers after the third dose will also be investigated using RCC.

***Antibodies against PT, FHA and PRN***

The percentage of subjects with seropositive levels of anti-PT, anti-FHA and anti-PRN (proportion of subjects with antibody titers greater than or equal to 5 EU/ml) with 95% CI will be determined at each blood sampling time point (all groups). Antibody titers will be summarized by GMT with 95% CI at all time points at which serological samples are taken. Vaccine response to anti-PT, anti-FHA and anti-PRN following vaccination will

be tabulated with 95% CIs. Antibody titers after the third dose will also be investigated using RCC.

The 95% CI of the GMT ratio (HEP[Ro]<sub>s</sub> + HERo[P]<sub>s</sub> groups over REP[Ro]<sub>s</sub> + RERo[Po]<sub>s</sub> + RE[RoP]<sub>s</sub> groups) will be calculated one month post Dose 3 of DTPa/Hib vaccine. If the upper limit of this CI is below 2, non-inferiority will be concluded.

#### **10.7.2.2.2. Analysis of safety**

Safety will be analyzed on the TVC.

The proportion of subjects with an SAE, classified by the MedDRA preferred term level, reported from study start until Month 8 (8 months post Dose 1 of RTS,S/AS01<sub>E</sub> or *Engerix-B*) will be tabulated with exact 95% CI.

Withdrawal due to SAE/AEs will be described in detail.

The proportion of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period (7 days) will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated over the entire vaccination course, with exact 95% CI.

The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period (7 days) will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated, overall and by vaccination course, with exact 95% CI.

For all solicited symptoms, the same tabulation will be performed for Grade 3 AEs and for AEs with relationship to vaccination.

The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA), whenever available, and reported up to 30 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.

## **11. ADMINISTRATIVE MATTERS**

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

**11.1. Case Report Form/Remote Data Entry instructions*****Case Report Form Instructions***

CRFs (and subject diary cards, if applicable), will be supplied by GSK Biologicals for recording all data.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed CRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent in-house CRF review may necessitate clarification or correction of data or omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases the investigator remains accountable for the study data collected.

Any questions or comments related to the CRF should be directed to the assigned Site Monitor.

The investigator will keep a paper copy of each CRF and any data query forms of the final version of the data generated at the investigational site.

***Remote Data Entry instructions***

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

**11.2. Monitoring by GSK Biologicals**

Monitoring visits by a GSK Site Monitor are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent

with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a CRF/ RDE review and a Source Document Verification (SDV). By SDV we mean verifying CRF/ RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the CRF/ RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the CRF/ RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF/eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

**11.3. Archiving of data at study sites**

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic for studies with an eCRF); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the Sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

**11.4. Audits**

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

**11.5. Posting of information on Clinicaltrials.gov**

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

**11.6. Ownership, confidentiality and publication****11.6.1. Ownership**

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

**11.6.2. Confidentiality**

Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

**11.6.3. Publication**

For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a 'Publication'), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least twenty-one working days, or at least fifteen working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

**11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

The results summary will be posted to the GSK Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

**12. COUNTRY SPECIFIC REQUIREMENTS**

Not applicable.

**13. REFERENCES**

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**CONFIDENTIAL**

113681 (MALARIA-063)  
Report (Immunogenicity and safety combined Month 3 and Month 8) Final

**CONFIDENTIAL**

113681 (Malaria-063)  
Administrative change 1

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## APPENDIX A LABORATORY ASSAYS

As serum represents approximately 50% of whole blood.

After blood centrifugation and serum separation, samples will be stored at -20°C until collection by the Sponsor. The aliquots of serum will be sent to GSK Biologicals for the tests described in the following paragraphs.

### ***Antibody levels against CS***

Antibody levels against CS will be measured at CEVAC (or a validated laboratory designated by GSK Biologicals) by standard ELISA methodology using plate adsorbed R32LR antigen with a standard reference antibody as a control according to SOPs from the laboratory. Results will be reported in EU/ml.

### ***Antibody levels against HBsAg***

Antibody responses against hepatitis B virus surface antigen (HBsAg) will be quantified at CEVAC using an in-house validated sandwich ELISA. Results are expressed in mIU/ml, and the cut-off for seroprotection is 10 mIU/ml.

### ***Antibody levels against HB RF1-like antibodies***

RF1-like antibodies will be measured at CEVAC using an in-house developed competitive ELISA with plate adsorbed HBs antigen. Dilutions of the test samples and the reference serum are mixed with a fixed amount of RF1 monoclonal antibody (mAb). The amount of antibody competing with RF1 mAb for binding to HBsAg is quantified by comparison with the reference serum according to SOPs from the laboratory. The results are expressed in ELISA Units per milliliter (EU/ml).

### ***Measurement of rotavirus IgA Antibodies by ELISA***

This assay allows the detection of rotavirus IgA in human serum and was initially designed by R. Ward [Bernstein 1998; Bernstein 1999]. It will be used for measuring the immune response after vaccination and/or infection. Samples will be analyzed at GSK Biologicals, Rixensart, Belgium (or a validated laboratory designated by GSK Biologicals). IgA antibody responses against rotavirus antigen will be quantified using an in-house validated sandwich ELISA. Results are expressed in U/ml, and the cut-off for seroprotection is 20 U/ml.

### ***Pneumococcal ELISA test***

Pneumococcal serotype specific total IgG antibodies (antibodies to 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) will each be measured by 22F-inhibition ELISA [Concepcion 2001; Henckaerts 2006]. The antibody concentration will be determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF available from the US Food and Drug Administration (FDA) for which concentration of IgG and IgM to the 10 serotypes are known in µg/ml [Quataert 1995]. The cut-off of the assay is 0.05 µg/ml.

***Pneumococcal opsonophagocytic activity***

*S. pneumoniae* opsonophagocytic activity will be measured by a killing-assay using a HL 60 cell line [Romero-Steiner 1997; Henckaerts 2007]. The results will be presented as the dilution of serum (opsonic titer) able to sustain 50 % killing of live pneumococci under the assay conditions. The cut-off of the assay is an opsonic dilution of 8.

***Pneumococcal protein D***

Anti-PD antibodies will be determined using an ELISA assay developed by GSK Biologicals. Concentration of specific PD antibodies will be determined, using a reference serum. The cut-off of the assay is 100 EU/ml.

***Antibody levels against acellular B pertussis antigens (anti-PT, anti-FHA, anti-PRN)***

Specific antibodies against diphtheria toxoid will be measured by ELISA techniques or multiplex techniques (Luminex technology). The cut-off of the test is 0.1 IU/ml. [Camargo, 1984]. Pre-booster samples with anti-diphtheria concentrations <0.1 IU/ml will be measured by the Vero-cell neutralisation test for which the cut-off is 0.016 IU/ml. Antibody concentrations greater than or equal to this value are considered as protective [Camargo, 1984].

Specific antibodies against tetanus toxoid will be measured by ELISA techniques [Melville-Smith, 1983] or multiplex techniques (Luminex technology). The cut-off of the test is 0.1 IU/ml.

IgG antibodies against the pertussis antigens (pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]) will be measured by ELISA techniques or multiplex techniques (Luminex technology). The cut-off of the tests is 5 EI.U/ml [Karpinsky, 1987; Granström, 1987; Sato, 1982].

**APPENDIX B AMENDMENTS AND ADMINISTRATIVE  
CHANGES TO THE PROTOCOL**

<b>GlaxoSmithKline Biologicals</b> Clinical Research & Development <b>Protocol Administrative change 1</b>				
<b>eTrack study number and Abbreviated Title:</b>		1136818 (MALARIA-063)		
<b>Administrative change number:</b>		Administrative change 1		
<b>Administrative change date:</b>		22 November 2011		
<b>Co-ordinating author:</b>		PPD Project Manager Scientific Writer Malaria Vaccines		
<b>Rationale/background for changes:</b> Some typographical errors were corrected for clarity:				
<ul style="list-style-type: none"> <li>In Synopsis table 1 and in Table 3 : the footnote of Rotarix in the RE[RoP]<sub>s</sub> group was corrected (should be footnote <b>b</b> and not <b>c</b>)</li> </ul>				
RE[RoP] <sub>s</sub>	RE[RoP] <sub>s</sub> lot 1 RE[RoP] <sub>s</sub> lot 2 RE[RoP] <sub>s</sub> lot 3	RTS,S/AS01E <sup>a</sup> + CoAd ( <i>Infanrix</i> /Hib <sup>a</sup> + <i>Polio Sabin</i> <sup>a</sup> ) + staggered ( <i>Synflorix</i> <sup>d</sup> + <i>Rotarix</i> <sup>b</sup> )		141 (47+47+47)
<ul style="list-style-type: none"> <li>The volume of the reconstituted <i>Rotarix</i> is 1.0 ml. It was erroneously recorded as 1.5 ml in table 15 and in the heading of section 6.3.5. and has been corrected.</li> </ul>				
<b>Vaccine</b>	<b>Formulation</b>	<b>Presentation</b>	<b>Volume</b>	<b>Number of doses</b>
<i>Rotarix</i>	Rotarix contains not less than 10 <sup>6.0</sup> CCID50 (Cell Culture Infectious Dose 50%) of live attenuated human rotavirus RIX4414 strain. The excipients of Rotarix (oral) comprise sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM), calcium carbonate, xanthan and sterile water.	It is presented as powder in a glass container and an oral applicator containing the diluent.	<del>1.5</del> 1.0 ml	2
<b>6.3.5 Rotarix (<del>1.5</del> 1.0 ml dose)</b>				
<ul style="list-style-type: none"> <li>Infanrix is administered in the right deltoid as described in Table 16. In section 6.3.4. this was mistakenly mentioned in the left deltoid and has been corrected.</li> </ul>				
<b>6.3.4. <i>Infanrix/Hib</i> (0.5 ml dose)</b>				
In order to ensure proper intramuscular injection of the study vaccines, a needle of at least 1 inch (2.54 cm) length, 25 gauge will be used. The vaccine will be administered as an intramuscular injection into the <del>left</del> <b>right</b> deltoid.				
<b>Corrected text has been indicated in <i>bold italics</i>, deletions are indicated by strikethrough.</b>				


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### Protocol Sponsor Signatory Approval

<b>eTrack study number and Abbreviated Title</b>	113681(Malaria-063)
<b>Date of protocol</b>	Final: 27 Aug 2010
<b>Detailed Title</b>	Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01 <sub>E</sub> candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.
<b>Sponsor signatory</b>	Amanda Leach, Director, Global Clinical R&D
<b>Signature</b>	
<b>Date</b>	10/09/10

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GlaxoSmithKline

## NOTE TO FILE

Alias / Abbreviated Study Title (if applicable)	MALARIA-063
E-Track Study Number (if applicable)	113681
Site ID (if applicable)	PPD

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
<b>Initial Incident/Issue</b>	No version control indicator (checksum) present on the translation compliance form for the translation of the study protocol into French
<i>Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.</i>	
<b>Cause of Incident/Issue</b>	Upon receipt of the Investigator Agreement page extracted from the French translation of the protocol and signed by Dr. PPD it was noted that the translation compliance form produced to document the translation of the protocol into French did not contain any version control indicator (e.g. the checksum) of the original Protocol.
<b>Consequence(s) of Issue/incident</b>	NA
<b>Corrective Action(s) with justification and timeline(s) for completion</b>	<p>This file note aims to certify that the French translation of the protocol from which the signed Investigator Agreement page is extracted was based on the original study Protocol identified by the following version control indicator :</p> <p style="text-align: center;">-----Checksum-----!Ver.!Created On - -</p> <p style="text-align: center;">0c2200d638872690d90d4f80bc0c1d46 2.41 09/09/2010 17:18:50 -</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">27-AUG-2010 0c2200d638872690d90d4f80bc0c1d46</p>
<b>Outcome of Corrective Action(s)</b>	NA
<b>Reference document(s)</b>	<p>SOP-BIO-CLIN-1000 v03 &gt; Chapter 6. Procedure / 6.3. Development, Review, Approval, Archiving and Distribution of Protocols / Investigator agreement of the final Protocol :</p> <p><i>'N.B. If the Protocol is translated into a local language, the Investigator Agreement page may be signed in the local language. In this case the LSC should attach a copy of the translation compliance form, containing the version control indicator (e.g. the checksum) of the original Protocol, to the signed Investigator Agreement page.'</i></p>
<b>Additional Information appended to this Note To File</b>	NA

Please complete the signature panel below and include all stakeholders involved

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**NOTE TO FILE**

	Full Name and job function	Signature	Date
Author	PPD [redacted] Global Study Manager	PPD [redacted]	07 Dec 2011
Co-Author (if applicable)	PPD [redacted] Clinical Trial Assistant	[redacted]	06 Dec 2011
Reviewed by (if applicable)			
Approved by (if applicable)	PPD [redacted] Clinical Operations Manager West/Central Africa	[redacted]	06 Dec 11





### TRANSLATION COMPLIANCE FORM

Please fill in all sections of this form; Note NA on all sections which are Not Applicable

Please ensure that a written confidentiality agreement is available from the third party translators when they undertake the translations.

**eTrack study number and abbreviated title:**

113681 (Malaria-063)

#### Document details:

Document details:	Version Number	Date of original document	Date of translation version	Language of original document	Translated language requested
Investigator CV(s) (name of investigator)					
ERC-approval(s) (name of ERC)					
Protocol(s)					
Final Protocol	Final	27/08/2010	22/10/2010	English	French
ICF(s)					
Other(s), specify					

**Translation details:**

- Name and function of translator: VMA Consulting..  
 ..... V.M.A. CONSULTING sprl  
 ..... Medical Translation & Writing Agency  
 ➤ Address of translator or GSK site: ..... Chemin des Gravevcs, 3  
 ..... 1348 Louvain-la-Neuve - Belgium  
 ..... PPD  
 I, the undersigned, hereby certify that the referenced translated document is accurate, clear and consistent with the original one.  
 ..... PPD  
 ➤ Signature of translator: .....  
 .....  
 ➤ Date of translation(s): 22/05/2010  
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- This translation was/ these translations were reviewed for accuracy, consistency, and clarity with the original document(s) by:*
- Name and function of reviewer: ..... PPD ..... GSK  
 .....  
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 ..... PPD  
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 .....  
 ➤ Date of review: 12/07/2011  
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**Medical Review (if required by local regulations):**

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 .....  
 ➤ Address of reviewer or GSK site: .....  
 .....  
 ➤ Signature of Medical reviewer: .....  
 .....  
 ➤ Date of medical review: \_\_ / \_\_ / \_\_  
 ..... dd / mmm / yyyy



**Protocol Investigator Agreement**

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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**eTrack study number and  
Abbreviated Title**

113681(Malaria-063)

**Date of protocol**

Final: 27 Aug 2010

**Detailed Title**

Phase III randomized, open, controlled study to  
evaluate the immune response to the hepatitis B  
antigen of the RTS,S/AS01<sub>E</sub> candidate vaccine, when  
administered as primary vaccination integrated into  
an EPI regimen to infants living in sub-Saharan  
Africa.

**Investigator name**

TSIRI AGBENYEGA  
PPD

**Signature**

[Redacted Signature]

**Date**

3<sup>rd</sup> May 2011

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113681 (Malaria-063)  
Administrative change 1

**Protocol Administrative change 1 Sponsor Signatory Approval**

<b>eTrack study number and Abbreviated Title</b>	113681(Malaria-063)
<b>Date of administrative change</b>	<i>Administrative change 1 Final, 22 November 2011</i>
<b>Detailed Title</b>	Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01 <sub>E</sub> candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.
<b>Sponsor signatory</b>	Johan Vekemans, Director, Clinical Development, Malaria Vaccines PPD
<b>Signature</b>	 PPD
<b>Date</b>	<u>7/12/11</u>

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Administrative change 1

eTrack study number and  
Abbreviated Title

113681(Malaria-063)

Date of administrative  
change

*Administrative change 1 Final, 22 November 2011*

Detailed Title

Phase III randomized, open, controlled study to  
evaluate the immune response to the hepatitis B  
antigen of the RTS,S/AS01<sub>E</sub> candidate vaccine, when  
administered as primary vaccination integrated into  
an EPI regimen to infants living in sub-Saharan  
Africa.

Investigator name

*DR VAKA Innocent*

Signature

PPD

Date

*19 FEB 2012*

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Administrative change 1

**eTrack study number and Abbreviated Title** 113681(Malaria-063)

**Date of administrative change** *Administrative change 1 Final, 22 November 2011*

**Detailed Title** Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01E candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa.

**Investigator name** TSIRU AGBENYEGA  
PPD

**Signature** 

**Date** 10<sup>th</sup> MAY 2012

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